Estudio clínico y farmacocinético del tratamiento con litio durante el período perinatal

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ESTUDIO CLÍNICO Y FARMACOCINÉTICO DEL TRATAMIENTO CON LITIO DURANTE EL PERIODO PERINATAL

Memoria de tesis doctoral presentada por María Luisa Imaz Gurruchaga para optar al grado de doctora por la Universidad de Barcelona

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“Ametsik gabeko bizia, izarrik gabeko gaua”

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1 ACRÓNIMOS Y ABREVIATURAS

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ADME	Absorción, distribución, metabolización, excreción
AMPc	Monofosfato de adenosina cíclico
ARN	Ácido ribonucleico
AVP	Ácido valproico
BDNF	Factor neurotrófico derivado del cerebro
CYPP450	Sistema citocromo P450
CBZ	Carbamazepina
CI	Concentración de fármaco en el plasma infantil
CU	Cordón umbilical
CU/IM	Cociente cordón umbilical/madre intraparto
DS	Desviación estándar
DRL	Dosis relativa para el lactante
EMA	European Medicines Agency
FDA	Food and Drug Administration
FUR	Fecha de última regla
GABA	Ácido gamma-aminobutírico
GSK-3b	Glicógeno sintetasa 3 quinasa
GWAS	Estudio de asociación del genoma completo
IM	Intraparto madre
I/P	Cociente entre la concentración del fármaco entre el suero infantil y el materno
Li	Litio
L/P	Cociente entre la concentración del fármaco en la leche y en el suero materno
LoQ	Límite de cuantificación
LTG	Lamotrigina
PLLR	Pregnancy and Lactation Labelling Final Rule
PM	Peso molecular
TB	Trastorno bipolar
$T_{1/2}$	Semivida de eliminación
TFG	Tasa de filtración glomerular
UCIN	Unidad de cuidados intensivos neonatales
UGT	Uridina 5′-difosfoglucuronosiltransferasa
Vd	Volumen de distribución

2 GLOSARIO

Aborto. Interrupción de la gestación antes de la semana 20 de embarazo, contando desde el primer día del último período menstrual. Según el momento en el que se produce se cl
asifica como precoz (antes de la semana 12 de gestación) o tardío (entre la semana 12 y 20 de gestación).

Anomalía de Ebstein. Cardiopatía congénita compleja caracterizada por el adosamiento de los velos valvulares tricúspideos posterior y septal al endocardio ventricular derecho, lo que condiciona el desplazamiento del orificio valvular hacia la porción apical del ventrículo derecho, dando por resultado una atrialización de dicho ventrículo. Puede ser reconocido en el período fetal mediante una ecocardiografía fetal. Las características hemodinámicas se definen en el período posnatal y su tasa de mortalidad total en el período perinatal es del 85%. Se presenta en 1-5 por cada 200.000 nacidos vivos y supone un 0,6% de las cardiopatías congénitas.

Bajo peso al nacer. Se caracteriza por un peso fetal inferior a 2.500 gr al momento del parto, contrasta con el peso promedio de alrededor de 3.500 gr.

Bajo peso para la edad gestacional. Son aquellos recién nacidos cuyo peso es < al percentil 10 para la edad gestacional. Las complicaciones asociadas son asfixia perinatal, aspiración de meconio, policitemia e hipoglucemia.

Biodisponibilidad oral. Es el porcentaje de la dosis administrada de un medicamento que llega intacto al sistema circulatorio. Este concepto es especialmente importante cuando se comparan diferentes formas de administración, como vía oral, intravenosa o transdérmica.
Diabetes gestacional. Cualquier grado de intolerancia a la glucosa, que es reconocido o identificado por primera vez en el embarazo.

Hipertensión gestacional. Aparición de durante la gestación de cifras de tensión arterial >140/90 que no se acompaña de proteinuria.

Infertilidad. Enfermedad del aparato reproductor definida por la imposibilidad de lograr un embarazo clínico después de 12 meses o más de relaciones sexuales sin protección regular

Macrosomia. Recién nacido que es mucho más grande que el promedio o aquel que pesa al nacer más de 4000 gr, independientemente de la edad gestacional.

Parto distócico. Parto en el que se realizan maniobras (p.ej. forceps) o intervenciones quirúrgicas (p.ej: cesárea).

Parto pretérmino. Es aquel que se da antes de las 37 semanas completas de gestación. En función de la edad gestacional se define como prematuridad extrema (parto antes de semana 28), grave (parto entre las semanas 28-32), moderada (parto entre las

semanas 32-34). leve (parto entre las semanas 34-37). Representan el 7-9% de los partos.

Polihidramnios. Es la acumulación excesiva de líquido amniótico, el líquido que envuelve al bebé en el útero durante el embarazo. Esta afección se presenta en un 1 % al 2 % de los embarazos y la mayoría de las veces es leve. Suele aparecer en la mitad del embarazo o al final

Preeclampsia. Aparición de hipertensión arterial (TA >140/90) y proteinuria (>300 mg/24 horas) después de la semana 20 de gestación. Tiene una prevalencia de 3-10% de los embarazos.

Semivida de eliminación. El tiempo que ha de pasar para que el fármaco se elimine a la mitad de sus valores originales.
Sufrimiento fetal agudo. Llamado también **distrés fetal**, se refiere a un estado que que altera la fisiología fetal antes o durante el parto, de tal modo que es probable su muerte o la aparición de lesiones permanentes en un período relativamente breve. En general es causado por un déficit de oxígeno secundario principalmente a insuficiencia en la circulación útero-placentaria, compresión del cordón umbilical y complicaciones fetales como la sepsis o las hemorragias.

Test de Apgar. Índice que permite una evaluación del estado fisiológico del recién nacido a los minutos 1,5 y 10 de vida. La prueba evalúa 5 parámetros: frecuencia cardiaca, respiración, tono muscular, reacción ante los estímulos y coloración de la piel. El rango de puntuación es de 0 a 10. Una puntuación inferior a 7 indica dificultades en el proceso de adaptación neonatal y requiere observación por parte de Neonatología.
Volumen de distribución. Es un volumen aparente (no real) y se define como el volumen que debería ocupar el fármaco para que en cada sitio del organismo su concentración sea equivalente a su concentración en la sangre.

3 LISTADO DE ARTÍCULOS QUE CONFORMAN LA TESIS

La presente tesis doctoral ha sido realizada en formato de compendio de publicaciones. La tesis consta de un objetivo general y siete objetivos específicos. Para lograr estos objetivos se han incluido cuatro artículos.

1. **Imaz ML**, Torra M, Langohr K, Poch E, Soy D, Garcia-Esteve Ll, Vieta E, Martin-Santos R. *How does pregnancy affect drug disposition of lithium? A retrospective observational cohort study.*
   Manuscrito sometido a revisión

2. **Imaz ML**, Torra M, Langohr K, Arca G, Soy D, Hernández AS, Garcia-Esteve Ll, Vieta E, Martin-Santos R. *Peripartum lithium management: early maternal and neonatal outcomes.* J Affect Dis 2024; 366:326-334.
   FI:4,9 Cuartil: Q1 Categoría: Psiquiatría

3. **Imaz ML,** Soy D, Torra M., Garcia-Esteve Ll, Soler C, Martín-Santos R. *Case report: Clínical and pharmacokinetic profile of lithium monotherapy in exclusive breastfeeding. A follow-up case series*. Front Pharmacol. 2021;24(12): e647414.
   FI: 5,6 Cuartil: Q1 Category: Farmacología y Farmacia

4. **Imaz ML,** Langohr K, Torra M, Soy D, Garcia-Esteve Ll, Martín-Santos R. *Neonatal feeding trajectories in mothers wit bipolar disorder taking lithium: pharmacokinetic data.* Front Pharmacol. 2021;22(12): e752022.
   FI: 5,6 Cuartil: Q1 Categoría: Farmacología y Farmacia

4 RESUMEN DE LA TESIS

4.1 THESIS SUMMARY

Title: “Clinical and pharmacokinetic study of lithium treatment during the perinatal period”

Background

Lithium is a first-line treatment for perinatal bipolar disorder. Although the concern with lithium use in pregnancy is teratogenicity, the risk-benefit balance is inclined towards its maintenance to prevent maternal relapses. Lithium is eliminated almost by the kidneys. Renal changes during pregnancy could be responsible for pharmacokinetic alterations that would affect the efficacy and toxicity of lithium in the mother-child dyad. A reduction in lithium dosage of 30-50% or its discontinuation 24-48 hours before delivery has been proposed to minimize neonatal complications. Most breastfeeding guidelines recommend that women treated with lithium should not breastfeed.

Hypothesis

1) Physiological renal changes during pregnancy, obstetric complications and the type of breastfeeding will be responsible for changes in lithium disposition, which may affect its clinical efficacy and contribute to toxicity in the mother-child dyad. 2) A brief peripartum discontinuation of lithium treatment will be associated with small fluctuations in maternal lithemia that will not compromise its efficacy, minimizing the risk of maternal and neonatal toxicity. 3) Placental transfer of lithium will be greater than that which occurs through breast milk. 4) Infants exposed to lithium in utero and through breast milk will not present lithium accumulation.

Aims

To characterize lithium disposition during the perinatal period and its clinical/analytical impact on the mother-child dyad. To study: 1) whether changes in maternal lithium levels are consistent with renal function (creatinine). 2) Changes in maternal lithium levels following a brief peripartum interruption, placental transfer of lithium, and the association between neonatal lithium levels at delivery and acute neonatal outcomes. 3) Clinical and pharmacokinetic characteristics of dyads exposed to lithium monotherapy at the end of pregnancy and during exclusive breastfeeding. 4) The behaviour of neonatal/infant lithemia based on the breastfeeding history.

Material and Methods

Observational, cohort, retrospective study in the perinatal psychiatry unit of a university hospital (2006-2018) (CEIC: HCD/2020/1305). 1) Socio-demographic/clinical/obstetric/ analytical/neonatal data were collected from the medical records of pregnant women treated with lithium, with at least one lithemia obtained at steady state and at pre-dose and creatininemia obtained simultaneously. The data obtained were analysed using linear mixed models. 2) Women treated with lithium in the peripartum period, with at least one maternal and neonatal lithemia at delivery, were investigated. Lithium was discontinued at the onset of labour or 12 hours before a scheduled delivery and restarted 6-12 hours postpartum. Data were analysed using Student's t test and Pearson correlation. 3) The lithemias and creatininemias of mother-child dyads exposed to lithium monotherapy at delivery and exclusively breastfeeding (days 1-5/7-11/30/60 postpartum and monthly up to 6 months) were analysed. 4) Women on lithium monotherapy and their neonates/infants, with different breastfeeding trajectories, were studied through multivariate analysis adjusting for lithemia at birth.

Results

1) A total of 1260 lithemias and 1326 creatininemias from 109 pregnancies in 95 women were analysed. The mean lithemia was estimated using a mixed model including dose and time as predictors. For a dose of 1000 mg/day, lithium concentration decrease an average of 30,2% (95%CI: 25,2%, 35,4%) during first trimester, 29,7% (25,2%, 34%) second trimester, and 20,6% (16,4%, 23,7%) in the third, and increase 2,4% (-1,7%, 7%) and 0,3% (-4,6%, 5,6%) in the first, and second to forth postpartum trimester. The creatininemia showed a similar longitudinal pattern along pregnancy and postpartum. Repeated multiple correlations were statistically significant ($p < 0.05$) along pregnancy and postpartum. 2) 226 maternal and 66 neonatal lithemias from 66 mother-child dyads were included. Slight fluctuations in maternal lithemia around 0.20 mEq/L and an early postpartum recurrence of 6% were found. The mean (SD) intrapartum cord lithemia ratio (mother) was [1.10 (0,17)]. Transient acute complications were observed in 56% of neonates. Neonatal hypotonia was the most frequent. The mean lithemia was 0.178 mEq/L higher in neonates with hypotonia ($p = 0.028$). 3) In the nine mother-child dyads, placental transfer was complete [(1,13 (0,10)]. No woman presented symptoms of lithium intoxication postpartum, two neonates presented transient hypotonia (22%). Neonatal exposure to lithium was lower during lactation than in utero ($p < 0.05$). Lithium levels decreased from delivery to 44% in the first month postpartum, reaching 60% in the third

month postpartum. No alterations in neonatal development were observed in the follow-up period. One woman presented a psychotic manic decompensation at 45 days postpartum. 4) In 24 mother-child pairs, placental transfer of lithium was complete [1,12 (0,17)]. The mean times to LoQ (limit of quantification) were 6-8 days for formula feeding, 7-8 for mixed feeding, and 53-60 days for exclusive breastfeeding ($p = 0.037$). No lithium accumulation was observed in infants who were exclusively or mixed breastfed, nor were there any alterations in neonatal/infant development during follow-up.

Limitations

The retrospective nature and moderate size of the cohort of pregnancies without medical risk factors mean that the results cannot be generalized to all pregnant women treated with lithium. There was no control group of women with bipolar disorder without psychopharmacological treatment.

Conclusions

Creatinine showed a longitudinal pattern similar to lithium in the perinatal period. Placental transfer of lithium was complete. A brief interruption of lithium before delivery was associated with slight fluctuations in maternal lithium levels. Newborns exposed to lithium in utero had mild and transient acute effects. In infants of mothers treated with lithium, no accumulation of lithium or adverse effects on development was observed. We recommend simultaneous monitoring of monthly lithium and creatinine levels until the 30th week of gestation, continuing weekly until delivery and during the first postpartum period. In selected women with bipolar disorder, lithium therapy during pregnancy and lactation may be an appropriate option if combined with close monitoring of the dyad.

4.2 RESUMEN DE LA TESIS

Título: “Estudio clínico y farmacocinético del tratamiento con litio durante el período perinatal”

Introducción

El litio es un tratamiento de primera línea en el trastorno bipolar perinatal. Aunque la preocupación del uso de litio en el embarazo es la teratogenia, el balance riesgo-beneficio se inclina hacia su mantenimiento para prevenir recaídas maternas. El litio se elimina casi exclusivamente vía renal. Los cambios renales durante el embarazo serían responsables de alteraciones farmacocinéticas que afectarían la eficacia y toxicidad del litio en la diada madre-hijo. Se ha propuesto una reducción de la dosis de litio del 30-50% o su interrupción 24-48 horas antes del parto para minimizar las complicaciones neonatales. La mayoría de las directrices sobre lactancia recomiendan que las mujeres tratadas con litio no deben amamantar.

Hipótesis

1) Los cambios renales fisiológicos del embarazo, las complicaciones obstétricas y el tipo de lactancia materna serán responsables de los cambios en la disposición del litio pudiendo afectar a su eficacia clínica y contribuir a la toxicidad en la diada madre-hijo. 2) Una breve discontinuación periparto del tratamiento con litio se asociará a pequeñas fluctuaciones de la litemia materna que no comprometerán su eficacia, minimizando el riesgo de toxicidad materna y neonatal. 3) La transferencia placentaria de litio será superior que la que se produce a través de la leche materna. 4) Los lactantes expuestos a litio intraútero y a través de la leche materna no presentarán acumulación de litio.

Objetivos

Caracterizar la disposición de litio durante el período perinatal y su impacto clínico/analítico sobre la diada madre-hijo. Estudiar: 1) Si los cambios en la litemia materna son consistentes con la función renal (creatinina). 2) Los cambios en la litemia materna tras una breve interrupción periparto, la transferencia placentaria del litio y la asociación entre la litemia neonatal en el parto y los resultados neonatales agudos. 3) Las características clínicas y farmacocinéticas de las díadas expuestas a litio en monoterapia al final del embarazo y durante la lactancia materna exclusiva. 4) El comportamiento de la litemia neonatal/lactante en función de la trayectoria de lactancia.

Material y Métodos

Estudio observacional, de cohorte, retrospectivo, en la unidad de psiquiatría perinatal de un hospital universitario (2006-2018) (CEIC: HCD/2020/1305). 1) Se recogieron datos sociodemográficos/clínicos/obstétricos/analíticos/neonatales de las historias clínicas de embarazadas tratadas con litio, con al menos una litemia obtenida en estado estacionario y en pre-dosis y creatininemias obtenidas simultáneamente. Los datos analíticos se analizaron mediante modelos lineales mixtos. 2) Se investigaron mujeres tratadas con litio en el periparto, con al menos una litemia materna y neonatal en el parto. El litio se suspendió al inicio del trabajo de parto o 12 horas antes de un parto programado, reiniciándose 6-12 horas posparto. Los datos se analizaron mediante la t-Student y la correlación de Pearson. 3) Se analizaron las litemias y creatininemias de las diadas madre-hijo expuestas a litio en monoterapia en el parto y lactancia materna exclusiva (días 1-5/7-11/30/ 60 días posparto y mensualmente hasta los 6 meses). 4) Se estudiaron mujeres en monoterapia con litio y sus neonatos/lactantes, con diferentes trayectorias de lactancia, mediante análisis multivariante ajustando por litemia al nacer.

Resultados

1) Se analizaron 1260 litemias y 1326 creatininemias de 109 embarazos en 95 mujeres. La litemia media fue estimada mediante un modelo mixto incluyendo la dosis y el tiempo como predictores. Para una dosis de 1000 mg/día, la concentración de litio disminuyó en el embarazo un promedio del 30,2% (IC95%=25,2%-35,4%) en el primer trimestre, 29,7% (IC95%=25,2%-34%) en el segundo, 20,6% (IC95%=16,4%-23,7%) en el tercero, y aumentó en el posparto un 2,4% (IC95%=-1,7%-7,1%) y 0,3% (IC95%=-4,6%-5,6%) en el primer y segundo-cuarto trimestre, respectivamente. La creatinina evidenció un patrón longitudinal similar al litio y a la ratio concentración/dosis de litio. 2) Se incluyeron 226 litemias maternas y 66 neonatales de 66 díadas madre-hijo. Se encontraron ligeras fluctuaciones de la litemia materna cercanas a 0,20 mEq/L y una recaída posparto temprana del 6%. La relación media (DE) de litemia intraparto del cordón umbilical/madre fue de 1,10 (0,17). Se observaron complicaciones agudas transitorias en un 56% de los neonatos. La hipotonía neonatal fue la más frecuente. La litemia media fue 0,178 mEq/L mayor en los neonatos con hipotonía (p=0,028). 3) En las nueve diadas madre-hijo, la transferencia placentaria fue completa [1,13 (0,10)]. Ninguna mujer presentó síntomas de intoxicación por litio posparto, dos neonatos presentaron hipotonía transitoria (22%). La exposición neonatal al litio fue menor durante la lactancia que

intraútero ($p<0,05$). Las litemias disminuyeron desde el parto hasta un 44% el primer mes posparto, alcanzando el 60% al tercer mes posparto. No se observaron alteraciones en el desarrollo neonatal en el período de seguimiento. Una mujer presentó una descompensación maníaca psicótica a los 45 días posparto. 4) En 24 parejas madre-hijo, la transferencia placentaria del litio fue completa [1,12 (0,17)]. Los tiempos medios hasta el LoQ (límite de cuantificación) fueron de 6-8 para la lactancia con fórmula, 7-8 para la mixta y 53-60 días para materna exclusiva ($p=0,037$). No se observó acumulación de litio en lactantes de lactancia materna exclusiva o mixta ni alteraciones en el desarrollo neonatal/lactante durante el seguimiento.

Limitaciones

El carácter retrospectivo y el moderado tamaño de la cohorte de embarazos sin factores de riesgo médico hacen que los resultados no sean generalizables a todas las embarazadas tratadas con litio. No se contó con un grupo control de mujeres con trastorno bipolar sin tratamiento psicofarmacológico.

Conclusiones

La creatinina evidenció un patrón longitudinal similar al litio en el período perinatal. La transferencia placentaria del litio fue completa. Una breve interrupción del litio preparto se asoció con ligeras fluctuaciones de la litemia materna. Los recién nacidos expuestos *intraútero* a litio presentaron efectos agudos leves y transitorios. En lactantes de madres tratadas con litio no se observó acumulación de litio ni efectos adversos sobre el desarrollo. Recomendamos realizar una monitorización simultánea de las litemias y creatininemias mensuales hasta la semana 30 de gestación, continuar semanalmente hasta el parto y durante el primer mes posparto. En mujeres seleccionadas con trastorno bipolar, la terapia con litio durante el embarazo y la lactancia puede ser una opción adecuada si se combina con una estrecha monitorización de la díada.

4.3 RESUM DE LA TESI

Títol: “Estudi clínic i farmacocinètic del tractament amb liti durant el període perinatal”

Introducció

El liti s’utilitza com a tractament de primera línia en el trastorn bipolar perinatal. Tot i que la principal preocupació de l’ús de liti durant l’ embaràs és la teratogènia, la balança risc-benefici s’inclina cap al manteniment del tractament per tal de prevenir recaigudes en la mare. El liti s’elimina gairebé de forma exclusiva per via renal. Els canvis renals durant l’embaràs serien responsables d’ alteracions farmacocinètiques que afectarien l’eficàcia i la toxicitat del liti a la diada mare-fill. S’ha proposat reduir la dosi de liti entre un 30-50%, o interrompre-la 24-48 hores abans del part per tal de minimitzar les complicacions neonatals. La majoria de les directrius sobre lactància recomanen que les dones tractades amb liti no haurien d’alletar.

Hipòtesis

Els canvis renals fisiològics ocorreguts durant l‘embaràs, les complicacions obstètriques i el tipus de lactància materna seran responsables dels canvis en la disposició del liti, podent afectar la seva eficàcia clínica i contribuir a la toxicitat en la diada mare-fill. 2) Una discontinuació breu del tractament amb liti, durant el peripart, s’associarà amb petites fluctuacions de la litèmia materna que no comprometran l’eficàcia, minimitzant el risc de toxicitat materna i neonatal. 3) La transferència placentària de liti serà superior que la que te lloc a través de la llet materna. 4) Els lactants exposats a liti intrauter i a través de la llet materna no presentaran acumulació de liti.

Objectius

Caracteritzar la disposició del liti durant el període perinatal i el seu impacte clínic/analític sobre la diada mare-fill. Estudiar: 1) Si els canvis en la litèmia són consistents amb la funció renal (creatinina). 2) Els canvis en la litèmia materna després d’ una breu interrupció peripart, la transferència placentària del liti i l’associació entre el liti neonatal en el part i els resultats neonatals aguts. 3) Les característiques clíniques i farmacocinètiques de les diades exposades a liti en monoteràpia al final de l’ embaràs i durant la lactància materna exclusiva. 4) El comportament de la litèmia neonatal/lactant en funció del tipus de lactància materna/fórmula/mixta.

Material i Mètodes

Estudi observacional, de cohort, retrospectiu, a la unitat de psiquiatria perinatal d'un hospital universitari (2006-2018) (HCD/2020/1305). 1) Es van recollir dades sociodemogràfiques/ clíniques/ obstètriques/ neonatals de les histories clíniques de dones embarassades tractades amb liti, amb com a mínim una litèmia extreta en estat estacionari i en pre-dosi, i amb creatinines obtingudes simultàniament. Les dades analítiques es van analitzar mitjançant models lineals mixtes. 2) Es van investigar dones tractades amb liti durant el peripart, amb almenys una litèmia materna i neonatal durant el part. El liti es va suspendre a l'iniciar el treball de part, o 12 hores abans d'un part programat, i es va reiniciar a les 6-12 hores postpart. Les dades es van analitzar mitjançant la t de Student i la correlació de Pearson. 3) Es van analitzar les litèmies i les creatinines de les diades mare-fill exposades a liti en monoteràpia durant el part i en lactància materna exclusiva (els dies 1-5/7-11/30/ 60 pospart i mensualment fins als 6 mesos). 4) Es van estudiar dones en monoteràpia amb liti i als seus nounats, amb diferents trajectòries de lactància, mitjançant anàlisi multivariant ajustant per litèmia al nàixer.

Resultats

1) Es van analitzar 1260 litèmies i 1326 creatinines en sèrum de 109 embarassos en 95 dones. La litèmia mitjana es va estimar mitjançans un model mixt incloent-hi la dosi i el temps com a predictors. Per una dosi de 1000 mg/día, la concentració de liti va disminuir durant l'embaràs un promig del 30,2% (IC95%=25,2%-35,4%) en el primer trimestre, 29,7% (IC95%=25,2%-34%) en el segon, 20,6% (IC95%=16,4%-23,7%) en el tercer, i va augmentar en el postpart un 2,4% (IC95%=-1,7%-7,1%) i un 0,3% (IC95%=-4,6%-5,6%) en el primer i segon-quart trimestre, respectivament. La creatinina va evidenciar un patró longitudinal similar al liti i la ratio concentració/dosi de liti. 2) Es van incloure 226 litèmies maternes i 66 neonatals de 66 diades mare-fill. Es van trobar lleugeres fluctuacions de la litèmia materna properes a 0,20 mEq/L i una tassa de recaiguda postpart primerenca del 6%. La relació mitjana (DE) entre la litèmia de la mare intrapart i la del cordó umbilical va ser de 1,10 (0,17). Es van observar complicacions agudes transitòries en un 56% dels nounats. L' hipotonia neonatal va ser la més freqüent. La litèmia mitjana va ser 0,178 mEq/L més alta en els nadons amb hipotonia en relació amb els que no la presentaven (p=0,028). 3) En les nou diades mare-fill, la transferència placentària va ser complerta [1,13 (0,10)]. Cap dona va presentar símptomes d'intoxicació per liti en el postpart, dos nounats van presentar hipotonia transitòria (22%). L' exposició neonatal al liti va ser menor durant la lactància que intraúter (p<0,05). El liti va disminuir fins un

44% el primer mes postpart, i fins un 60% al tercer mes postpart. No es van observar alteracions en el desenvolupament neonatal durant el període de seguiment. Una dona va presentar una descompensació maníaca psicòtica als 45 dies postpart. 4) En 24 parelles mare-fill, la transferència placentària de liti va ser complerta [1,12 (0,17)]. El temps mitjà per assolir el LoQ (límit de quantificació) va ser de 6-8 dies per lactància de fórmula, 7-8 per mixta i 53-60 per exclusiva (p=0,037). No es va observar acumulació de liti en lactants amb lactància materna exclusiva o mixta, ni alteracions en el desenvolupament neonatal/lactant durant el, seguiment.

Limitacions

El caràcter retrospectiu i la moderada mida de la cohort d'embarassos embarassos sense factors de risc mèdic fan que els resultats no siguin generalitzables a totes les embarassades tractades amb liti. No es va disposar d'un grup control de dones amb trastorn bipolar sense tractament farmacològic.

Conclusions

La creatinina ,en el període perinatal, va evidenciar un patró longitudinal similar al del liti. La transferència placentària de liti va ser complerta. Una interrupció breu del liti durant el prepart es va associar amb lleugeres fluctuacions de la litèmia materna. Els nounats exposats a liti *intraúter* van presentar efectes aguts freqüents, lleus i transitoris. En els lactants de mares tractades amb liti no es va observar acumulació de liti ni efectes adversos sobre el desenvolupament. Recomanem realitzar un monitoratge simultani mensual del liti i de la creatinina fins a la setmana 30 de gestació, i continuar setmanalment fins al part i durant el primer mes postpart. En dones seleccionades amb trastorn bipolar, la teràpia amb liti durant l'embaràs i la lactància pot ser una opció adequada si es combina amb un monitoratge estret de la diada.

4.4 TESIAREN LABURPENA

Izenburua: “Aldi perinatalean litio bidezko tratamenduaren azterketa klinikoa eta farmakozinetikoa"

Sarrera

Litioa erabili ohi da nahasmendu bipolarrean, lehen mailako tratamendu gisa aldi perinatalean. Litioa haurdunaldian erabiltzeari dagokion kezka nagusia teratogenia bada ere, arriskua-onura balantzea horri eustearen aldekoa da, ama berriro gaixotzeko arriskuari aurre egin ahal izateko. Litioa giltzurrunen bidez baino ez da kanporatzen. Haurdunaldian giltzurrunetan gertatzen diren aldaketak dira litioak amarengan eta haurrarengan duen eraginkortasunari eta toxikotasunari eragingo dioten aldaketa farmakozinetikoen eragileak. Litioaren dosia % 30-50 murriztea edo erditu baino 24-48 ordu lehenago etetea proposatu da, jaioberriengan arazoak minimizatzeko. Jarraibide gehienen gomendioa da litioa hartzen duten emakumeek bularrik ez ematea.

Hipotesiak

1) Haurdunaldian giltzurrunetan gertatzen diren aldaketa fisiologikoak, arazo obstetrikoak eta edoskitze mota dira litioaren antolaketan gertatzen diren aldaketen arduradunak, eta horrek eragina izan dezake haren eraginkortasun klinikoan eta lagun dezake, orobat, toxikotasunari ama-haurra diadan. 2) Erditze inguruko aldian litioaren tratamenduan etenaldi labur bat amaren litemiaren gorabehera txikiekin lotuko da, baina ez dute haren eraginkortasuna arriskuan jarriko, eta minimizatu egingo da toxikotasun-arriskua bai amarengan bai jaioberriarengan. 3) Litioaren plazenta bidezko transferentzia amaren esnearen bitartez gertatzen dena baino handiagoa izango da. 4) Umetoki barnean eta amaren esnearen bitartez litioarekiko esposizioa izandako bularreko haurrek ez dute litio pilaketarik izango.

Helburuak

Litioaren disposizioa aldi perinatalean eta hark ama-haurra diadan duen eragin kliniko/analitikoan duen eragina ezaugarritzea. Aztertzea: 1) Litemiaren aldaketak giltzurrunen funtzioarekin baduten loturarik (kreatinina). 2) Erditzean amaren litemian gertatuko aldaketak, litioaren plazenta bidezko transferentzia eta jaioberrien litemiaren eta jaioberrien emaitza akutuen arteko lotura, erditze inguruko etenaldi labur baten ondoren. 3) Jaioberrien litemia, edoskitze motaren arabera: amagandikoa/formula/mistoa. 4) Ama-haurren datu klinikoak eta farmakozinetikoak, litioaren monoterapiaren

eraginpean daudenean haurdunaldiaren eta amagandiko edoskitze esklusiboaren azken etapan.

Materiala eta Metodoak

Behaketa-azterketa, kohorte bidezkoa, atzera begirakoa, unibertsitate-ospitale bateko psikiatriako unitate perinatalean (2006-2018) (CEIC:HCD/2020/1305). 1) Litio tratamendua duten eta emakume haurdunen historia klinikoen datu soziodemografikoak, klinikoak, obstetrikoak eta neonatalak jaso ziren, egoera geldikorrean eta aurre-dosian lortutako litemia batekin gutxienez eta erauzketa berean lortutako kreatininemiekin. Datu analitikoak eredu lineal mistoen bidez aztertu ziren. 2) Erditzearen inguruko aldian litioarekin tratatutako emakumeak ikertu ziren, erditzean amak eta jaioberriak gutxienez litemia bat izanik. Litioaren tratamendua erditze lanarekin hastean edo programatutako erditze bat baino 12 ordu lehenago, eta erditzearen ondorengo 6-12 ordura ekin zitzaion berriro. Datuak t-Student eta Pearsonen korrelazioaren bidez aztertu ziren. 3) Litiodun monoterapiaren eraginpean egondako ama-jaioberrien diaden litemiak eta kreatininemiak aztertu ziren, erditzean eta soilik amarengandik edoskitzen dutenean, erditu eta 1-5, 7-11, 30 eta 60 egunetan, eta, hilero, 6 hilabete igaro arte. 4) Haurdunaldiaren azken etapan eta erditzearen ondoren (N = 8 tarte bakoitzeko) litiodun monoterapian egondako emakumeak aztertu ziren, eta baita haien haur jaioberriak, eta edoskitze mota ezberdinekin aldagai anitzeko analisi bat egin zen, litemiarekin doituz jaiotzean.

Emaitzak

1) 109 haurdunalditako 1260 litemia eta 1326 kreatininemia aztertu ziren 95 emakumerengan. Batez besteko litemia eredu misto baten bitartez balioetsi zen, dosia eta denbora harturik iragarle gisa. 1000 mg/eguneko dosi batean, litio-kontzentrazioa haurdunaldian % 30,2 murriztu zen batez beste lehenengo hiruhilekoan (KI%95=%25,2-%35,4), % 29,7 (KI%95=25,2-%34) bigarrenean eta % 20,6 (KI%95=%16,4-%23,7) hirugarrenean, eta erditzearen ondoko aldian %2,4 (KI%95=%-1,7-%7,1) eta %0,3 (KI%95=%-4,6-%5,6) igo zen lehenengo eta bigarren-laugarren hiruhilekoan, hurrenez hurren. Kreatininemiak agerian utzi zuen litioaren eta litio kontzentrazio/dosi ratioaren antzeko luzetarako patroia. 2) 66 ama-haur bikote sartu ziren eta 226 litemia lortu ziren amengan eta 66 jaioberriengan. Litemia fluktuazio arinak aurkitu ziren amengan 0,20 mEq/L inguruko, eta % 6ko gaixotze goiztiarra erditze ostean. Zilbor-heste/amaren litemiaren batez besteko erlazioa (DE) 1,10 (0,17) izan zen. Jaioberrien % 56ek aldi baterako arazo akutuak izan zituzten. Jaioberrien hipotonia izan zen ohikoena. Batez besteko litemia 0,178 mEq/L handiagoa izan zen hipotonia zutenengan hura ez

zutenengan baino (p = 0,028). 3). Ama-haurra bederatzi diadetan, litioaren transferentzia plazentarioa osoa izan zen [1,13 (0,10)]. Emakume bakar batek ere ez zuen litioak eragindako intoxikazio-sintomarik izan erditzearen ondoren; bi jaioberrik aldi baterako hipotonia izan zuten (% 22). Litioarekiko esposizioa txikiagoa izan zen jaioberriengan edoskitzaroan umetoki barnean baino (p < 0,05), eta litemiak % 44 murriztu ziren erditzetik lehen hilabetera arte, erditze ondoko hirugarren hilabetean % 60ra iristeraino. Jaioberrien garapenean ez zen ez gorabeherarik izan jarraipen-aldiari dagokionez. Emakume batek ezaugarri psikotikoak zituen deskonpentsazio maniako bat izan zuen erditze ostean, 45 egunera. 4) Ama-haurra 24 bikotetan, litioaren plazenta bidezko transferentzia osoa izan zen erditzean [1,12 (0,17)]. LoQra arteko (kuantifikazio-muga) batez besteko denbora 6-8, 7-8 eta 53-60 egunekoa izan zen amagandiko edoskitze denboran, formula, mistoarekin eta esklusiboarekin, hurrenez hurren (p=0,037). Amagandiko edoskitze esklusiboan edo mistoan zeuden haurrengan ez zen litiorik pilatu.

Mugak

Kohortearen, arrisku-faktore medikorik gabeko haurdunaldiak, atzera begirako izaeraren eta tamaina neurrizkoaren ondorioz, emaitzak ezin dira litioarekin tratatutako haurdun guztietara orokortu. Ez zen nahasmendu bipolarra zuten baina litioaren tratamendua hartzen ez zuten emakumeen kontrol-talderik eduki.

Ondorioak

Kreatininemiak litioaren antzeko luzetarako patroia adierazi zuen haurdunaldian. Litioaren plazenta bidezko transferentzia erabatekoa izan zen. Erditze aurreko litioaren etenaldi laburra amaren litemiaren gorabehera arinekin lotu zen. Umetoki barruan litioaren eraginpean zeuden jaioberriek eragin akutuak izan zituzten maiz, baina iragankorrak izan ziren. Litioarekin tratatutako amen bularreko haurren kasuan, ez zen ikusi litioaren metaketa jarraiturik, ezta ondorio kaltegarririk ere, ez garapenean ez hazkundean. Hilero, haurdunaldiaren 30 astera arte, hilero, litemien eta kreatininemien aldi bereko monitorizazioa egitea gomendatzen dugu, eta, astero, erditu arte eta erditu ondorengo lehen hilabetera arte. Nahasmendu bipolarra duten eta aldi perinatalean litio tratamenduan dauden emakume hautatuen kasuan, litio bidezko terapia haurdunaldian eta amagandiko edoskitzea aukera egokia izan daiteke ama-haurren monitorizazio zorrotzarekin konbinatzen bada.

5 INTRODUCCIÓN

5.1 FARMACOLOGÍA EN EL EMBARAZO, PARTO Y LACTANCIA

El uso de fármacos en el embarazo, parto y lactancia para el tratamiento de problemas médicos agudos (p.ej: náuseas y vómitos, fiebre, dolor, infección) o de patologías crónicas (p.ej: asma, diabetes, hipertensión arterial, depresión, trastorno bipolar) representa una situación clínica compleja. Debido a las dificultades éticas, medicolegales y de seguridad fetal y del lactante la información científica disponible sobre seguridad, efectividad y manejo de los fármacos en esta población es aún incompleta. Esta información procede fundamentalmente de estudios de cohortes, estudios de casos y controles, series de casos o casos únicos, datos de registro poblacionales y estudios preclínicos. En la práctica clínica diaria los profesionales de la salud continúan teniendo dificultades para interpretar y evaluar los beneficios y los riesgos de los fármacos (1).

Desde una perspectiva farmacocinética, hay pocos estudios que se hayan centrado en los cambios fisiológicos que tienen lugar durante el embarazo y la lactancia y quizá sea poco conocido que las mujeres cuando están embarazadas van a precisar ajustar las dosis de su medicación para evitar descompensaciones de su patología de base y/o intoxicaciones farmacológicas. Los fármacos atraviesan la barrera placentaria y se trasfieren a través de la leche materna, lo que puede significar un riesgo potencial para el feto/neonato/lactante. Elegir la dosis de fármaco adecuada para cada gestante es un equilibrio difícil ya que la necesidad de tratamiento farmacológico para el manejo de las patologías agudas y/o crónicas maternas debe sopesarse con el riesgo de la exposición fetal/neonatal/lactante al fármaco y/o a la enfermedad materna no tratada. Con frecuencia se ha considerado que la seguridad fetal/neonatal/lactante es más importante que la estabilidad materna (2).

5.1.1 Cambios farmacocinéticos durante el embarazo y la lactancia

La farmacocinética de los fármacos durante el embarazo y la lactancia debe considerarse en el contexto de dos unidades integradas de múltiples compartimentos: "unidad madre-placenta-membranas extra amnióticas-líquido amniótico-feto" y "unidad madre-leche-lactante". Los cambios farmacocinéticos maternos en combinación con la potencial trasferencia placentaria y la incipiente capacidad metabólica fetal y del neonato/lactante determinarán la exposición farmacológica fetal/neonatal/lactante. Estos cambios comienzan en el primer trimestre de gestación, son más marcados en el tercer trimestre y retornan gradualmente a la normalidad tras el parto, pudiendo dar lugar a una reducción o a un aumento de las concentraciones séricas de los fármacos administrados durante el embarazo (3).

5.1.1.1 Unidad materno-placento-fetal

Durante la etapa perinatal se producen en la mujer una serie de cambios fisiológicos adaptativos, transitorios y dinámicos que se traducen en modificaciones farmacocinéticas (ADME) de las distintas fases de ésta (absorción, distribución, metabolismo y excreción), que explican principalmente las diferencias en los perfiles farmacocinéticos de los fármacos entre mujeres embarazadas y no embarazadas (4).

Como resultado de los cambios inducidos por la progesterona en el músculo liso gástrico, el vaciamiento gástrico se retrasa y puede tener un impacto directo en la absorción del fármaco. Para la mayoría de los medicamentos administrados por vía oral, factores como el aumento del flujo sanguíneo gástrico e intestinal, el retraso en el tránsito intestinal, la actividad de los transportadores intestinales de fármacos y el pH del tracto gastrointestinal, afectan la absorción intestinal (5). El pH del estómago aumenta durante el embarazo a un rango alcalino tal que la absorción de fármacos básicos (p. ej., anfetaminas, metadona) disminuye mientras que la absorción de fármacos ácidos (p. ej.,

aspirina, fenitoína) aumenta (debido al aumento de la disociación iónica). A pesar de estos cambios gastrointestinales asociados en la absorción de fármacos, los estudios han sugerido que la biodisponibilidad y el impacto terapéutico de la mayoría de los medicamentos orales generalmente no se ven afectados por los cambios gastrointestinales durante el embarazo, especialmente cuando se repite la dosificación del fármaco (6). Para los fármacos administrados por vía parenteral (intramuscular, intravenosa y subcutánea), la absorción del fármaco aumenta durante el embarazo como consecuencia directa del aumento de flujo sanguíneo de la masa muscular debido al aumento del gasto cardíaco (7). Después de la absorción, la mayoría de los fármacos se distribuyen en diferentes tejidos corporales. El embarazo se asocia con cambios en el volumen de distribución (Vd) como resultado directo del aumento del volumen sanguíneo (aproximadamente un 50%), de la disminución de las proteínas plasmáticas disponibles y del aumento de las reservas de grasa corporal en el tejido subcutáneo. Estos cambios en el Vd de los fármacos pueden provocar alteraciones de las concentraciones máximas y mínimas de los fármacos (8). Si bien existen numerosos sitios para la biotransformación y el metabolismo de los fármacos (hígado, tracto gastrointestinal, riñones, piel, pulmones, plasma), el hígado es el sitio principal de la metabolización de fármacos. El embarazo afecta las fases I y II de metabolización hepática. Debido a la disminución en el embarazo de la actividad de las enzimas CYP1A2 y CYP2C19, disminuye el aclaramiento de los fármacos que son sustrato de estas enzimas, pudiendo aumentar potencialmente la toxicidad de los mismos. La actividad de las enzimas CYP3A4, CYP3A5, CYP2D6, uridina 5′-difosfoglucuronosiltransferasa (UGT) 1A4, UGT2B7 y CYP2E1 generalmente aumenta durante el embarazo, lo que provoca una disminución de las concentraciones plasmáticas de sus fármaco sustrato, que pueden llegar a ser subterapéuticos (9). Los riñones son el órgano principal para la eliminación de fármacos. Durante el embarazo normal se produce el aumento del flujo sanguíneo renal en un 60-80% y del filtrado glomerular en un 40-50%, lo que hace que aumente la excreción de los fármacos de eliminación renal y se requiera ajustar de dosis para evitar concentraciones plasmáticas subterapeúticas (10).

Los cambios fisiológicos en el embarazo junto a sus consecuencias farmacocinéticas sobre los fármacos se resumen en la **Tabla 1**.

Tabla 1. Cambios fisiológicos en el embarazo y consecuencias farmacocinéticas sobre los fármacos[a].

Etapa farmacocinética	Cambios fisiológicos	Efecto farmacocinético
Factores maternos		
Absorción	Disminución del pH salival Disminución de la acidez gástrica Enlentecimiento del vaciamiento gástrico Disminución de la motilidad intestinal Aumento del flujo sanguíneo local	Disminución de la absorción sublingual de fármacos ácidos Disminución de la absorción gastrointestinal de fármacos ácidos Ligero retraso en la absorción gastrointestinal del fármaco Aumento de la absorción intestinal del fármaco Aumento de la absorción intramuscular del fármaco
Distribución	Aumento del agua corporal total Aumento del volumen plasmático en un 50% al final del embarazo Disminución de la unión a proteínas Aumento de la grasa corporal en un 25% en el tejido subcutáneo	Aumento del volumen de distribución de los fármacos hidrosolubles Aumento de la fracción libre de fármaco Acumulación de los fármacos lipofílicos en el tejido adiposo
Metabolismo	Aumento de la actividad enzimática del CYP3A4, CYP2D6, CYP2C9 y UGT1A4 Disminución de la actividad enzimática del CYP1A2 y del CYP2C19	Disminución o incremento de la concentración sérica de los fármacos metabolizados por estas enzimas
Eliminación	Aumento del flujo sanguíneo renal en un 60-80% y del filtrado glomerular renal en un 40-50%	Aumento de la excreción de fármaco libre y disminución de su concentración sérica
Factores fetales		
Distribución	Bajas proteínas plasmáticas al principio de la gestación Altas proteínas plasmáticas al final de la gestación	Los niveles de fármaco libre en el feto disminuyen a lo largo de la gestación
Metabolismo	Capacidad metabólica hepática limitada Deglución del líquido amniótico	Acumulación de fármaco en el feto
Eliminación	Eliminación renal inmadura	Acumulación de fármaco en el feto

[a]Tabla creada por la autora.

La placenta es un órgano feto-materno con dos componentes: una parte fetal, desarrollada desde una parte del saco coriónico, y una parte materna, derivada del endometrio, membrana mucosa que incluye la capa más interna de la pared uterina. Es el nexo de unión y de intercambio entre la circulación materna y fetal. Realiza múltiples funciones dirigidas a promover el desarrollo y el crecimiento fetal, como la de trasferencia de sustancias, respiración, metabolización y de barrera. El desarrollo temprano de la placenta se caracteriza por la proliferación rápida del trofoblasto y el desarrollo del saco coriónico y las vellosidades coriónicas. Al final de la tercera semana se ha establecido la disposición anatómica de las distintas estructuras necesaria para los cambios fisiológicos que han de producirse entre la madre y el feto. Al final de la cuarta semana se desarrolla una compleja red vascular en la placenta que permite el intercambio de gases, nutrientes y productos metabólicos de desecho entre la madre y el feto (11).

El cordón umbilical es una estructura embriológica que conecta la placenta con el feto. Está conformado por un conjunto de vasos sanguíneos que se ubican dentro de una vaina tubular de amnios y consta de dos arterias y una vena umbilicales. Las arterias umbilicales tienen la función de transportar la sangre desoxigenada desde el feto a la placenta, mientras que la vena umbilical transporta sangre oxigenada desde la placenta hacia el feto hasta el parto (11).

La trasferencia placentaria de sustancias, incluidas los fármacos, está regulada por factores anatómicos, fisiológicos y bioquímicos:

1. Membrana placentaria: la membrana placentaria va perdiendo grosor con el curso del embarazo y la superficie placentaria va aumentando. Cuanto mayor sea la superficie de intercambio y menor grosor tenga la placenta, mejor será la difusión de los fármacos a través de ella.
2. Gradiente de concentración a través de la membrana placentaria: los fármacos pasan del lado más concentrado al menos concentrado por difusión pasiva. Por tanto, el fármaco pasa de la madre al feto.

3. Diferencia de presión hidrostática y osmótica a cada lado de la barrera placentaria: el tránsito de sustancias se produce del lado de mayor presión (materno) al de menor presión (fetal).
4. Flujo sanguíneo uterino: el flujo sanguíneo es mayor al final del embarazo, lo que favorece la trasferencia de nutrientes y fármacos a través de la placenta.
5. Tensión arterial materna: en la hipertensión arterial gestacional se estrecha la luz de las arterias maternas que atraviesan la placenta, dificultando el intercambio.
6. El pH: el pH del cordón umbilical es ligeramente más ácido que el de la sangre materna. Por consiguiente, se producirá un mayor atrapamiento de los fármacos básicos en el cordón umbilical, donde se encontrarán más ionizados.
7. En la placenta humana se han identificado un número variado de citocromos CYP P450 (CYP3A4, CYP1A2, CYP2B6) y UGT con capacidad de metabolización que limitan la exposición fetal a los fármacos presentes en la circulación materna (12).

Las propiedades fisicoquímicas de los fármacos que determinan su difusión a través de la placenta (11) se detallan a continuación:

1. Grado de liposolubilidad: a mayor liposolubilidad de un fármaco, mayor distribución a través de las membranas y mayor distribución hacia los tejidos con alto contenido lipídico. Las mujeres embarazadas presentan un aumento de su tejido adiposo y, por consiguiente, la distribución de los fármacos liposolubles es mayor.
2. Grado de ionización: la fracción ionizada, por su escasa liposolubilidad, no puede difundirse o lo hace escasamente a través de la membrana placentaria.
3. Peso molecular (PM): cuanto menor sea el peso molecular de un fármaco mejor se difundirá y atravesará la barrera placentaria. La mayoría de los fármacos con un peso molecular de < 500 dalton cruzan rápidamente la placenta e ingresan en la circulación fetal. Los fármacos que no cruzan la placenta aún pueden dañar al feto mediante diferentes mecanismos, tales como: la constricción de los vasos placentarios que perjudica el intercambio de gases y nutrientes, la producción de hipertonía uterina grave que produce lesiones anóxicas, y las alteraciones de la fisiología materna (ej.: causando hipotensión)

4. Unión a proteínas plasmáticas: la fracción de fármaco unida a proteínas plasmáticas no es capaz de difundir, actuar ni eliminarse por el organismo. La fracción libre de fármaco es la fracción activa farmacológicamente.

Una vez que han atravesado la placenta, los fármacos llegan al feto vía la sangre venosa umbilical y el 50% de esta sangre entre en la circulación hepática y el resto atraviesa el ducto venoso. La mitad del fármaco trasportado es susceptible de metabolismo hepático y la otra mitad ingresa a la circulación fetal directamente. La capacidad metabólica y de excreción del feto es mucho menor que la del adulto. Además, el feto puede reabsorber los fármacos o sus metabolitos activos a través de la deglución del líquido amniótico. Estos factores hacen que potencialmente se puedan acumular en el feto sustancias farmacológicamente activas. El cociente cordón umbilical/madre intraparto (CU/IM), que se calcula dividiendo la concentración del fármaco en el cordón umbilical por la concentración en el suero materno en el momento del parto, nos da una estimación de la trasferencia placentaria de un fármaco y nos proporciona una información valiosa acerca de la exposición fetal al fármaco (13). En general, el equilibrio entre las concentraciones séricas de fármaco en la sangre materna y los tejidos fetales necesita al menos 30 a 60 minutos. Sin embargo, algunos fármacos no alcanzarán concentraciones similares en la circulación materna y fetal.

5.1.1.2 Unidad madre-leche-lactante

La leche materna constituye el alimento natural ideal para los recién nacidos y los lactantes. Es una suspensión grasa en una solución de proteínas, de hidratos de carbono y de sales minerales. Es más ácida que el plasma (pH 6,8-7) e isoosmótica. Su composición varía según se trate de calostro (3-4 días de vida, pH 7,45, rico en vitamina K, proteínas, minerales, sodio y potasio), leche de transición (hasta la 3ª semana de vida, contenido creciente en azúcares y grasa) o leche completa (pH 7-7,1, de mayor contenido graso).

Para que un fármaco llegue de la madre al lactante, deberá seguir los siguientes pasos: pasar a la sangre materna, pasar a la leche materna, persistir en la leche materna en concentraciones significativas y pasar a la sangre del lactante. Los factores que determinan la excreción de los fármacos en la leche materna van a depender de las características del fármaco, así como de los factores relacionados con la madre y con el lactante (14). Ver **Figura 1.**

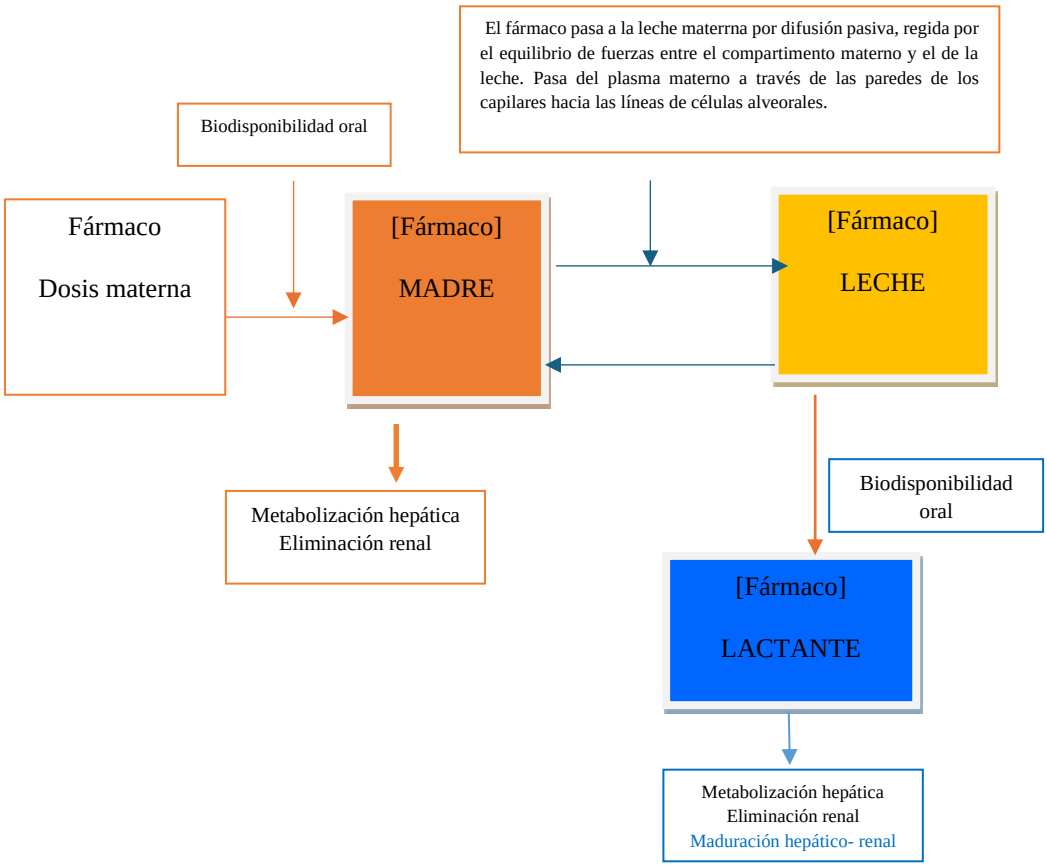


Figura 1. Transferencia del fármaco a través de la unidad madre-leche-lactante.

Para que un fármaco llegue de la madre al lactante, tras su absorción (p.ej., oral, parenteral) se distribuirá por los tejidos, pasando a la sangre materna, de ahí a la leche materna, persistir en la leche materna en concentraciones significativas y pasar a la sangre del lactante. Figura creada por la autora.

Las características del fármaco que determinan su excreción a través de la leche materna son:

1. Peso molecular (PM): los fármacos de peso molecular >500 daltons tienen más dificultad de paso a la leche materna y el paso de macromoléculas >700-800 Dalton es nulo.
2. Biodisponibilidad oral: los fármacos con baja biodisponibilidad oral, aunque lleguen a través de la leche materna, apenas son absorbidos por el lactante.
3. Unión a proteínas plasmáticas. La fracción libre de fármaco es la que se excretará a través de la leche materna. A mayor unión a proteínas del fármaco, habrá mayor dificultad de paso a la leche.
4. Liposolubilidad: los fármacos liposolubles pasan mejor a la leche materna.
5. Ionización; al ser la leche más ácida que el plasma, los fármacos básicos se excretan mejor en la leche materna respecto a los fármacos ácidos.

Los factores maternos que determinan la excreción de fármacos a través de la lecha materna son:

1. Composición de la leche: los fármacos lipofílicos se excretan en mayor concentración en la leche completa que en el calostro.
2. Cantidad de leche producida.
3. Alteraciones farmacocinéticas maternas: la insuficiencia hepática o renal materna, así como los fenotipos metabolizadores lentos, podrían determinar que aumentase la concentración sérica de un fármaco en la sangre materna y consecuentemente un mayor paso a la leche.
4. Dosis materna del fármaco.

Los factores del lactante que determinan la cantidad de fármaco que recibirá de la leche materna son:

1. Edad gestacional al nacer y la edad del lactante: a menor edad, mayor inmadurez en el metabolismo hepático y en la eliminación renal
2. Capacidad de succión del lactante y frecuencia de las tomas: el volumen de leche trasferido al lactante va desde los 20 ml el 1er día de vida a los 800 ml/día a los 6 meses de vida.
3. Factores farmacocinéticos del lactante: en los primeros días de vida el pH gástrico es más básico y los fármacos ácidos se absorben peor. La disminución de las proteínas plasmáticas y una menor afinidad por ellas conlleva una mayor cantidad de fármaco libre. Los sistemas hepáticos de glucuronidación y de oxidación no maduran hasta los tres meses de vida y representan el 20% de los del adulto. Por otra parte, la tasa de eliminación renal del fármaco es alrededor de una tercera parte de la del adulto.
4. Hiperbilirrubinemia del lactante. Los fármacos compiten con la bilirrubina por su unión a las proteínas plasmáticas. Si el fármaco desplaza las proteínas plasmáticas de su unión a bilirrubina el neonato podría presentar una encefalopatía bilirrubinémica (*kernicterus*).

5.1.1.2.1 Exposición del lactante a fármacos a través de la leche materna

Los métodos de estimación de la trasferencia de fármacos en la unidad madre-leche-lactante pueden ser directos (concentración de fármaco en el suero infantil) o estimados (cociente de concentración del fármaco entre la leche y el suero materno, dosis relativa para el lactante, cociente de concentración de fármaco entre suero infantil y suero materno):

1. Concentración de fármaco en el suero infantil (Índice I). La concentración de fármaco suero infantil proporciona información sobre la fracción de fármaco que está sistemáticamente disponible para el lactante (15). Es la medida más directa para la evaluación de riesgos (16,17,18). Sin embargo, en las mujeres que toman un fármaco al final del embarazo, los niveles séricos neonatales medidos en el período postparto temprano (primeros 7 a 10 días posparto)

pueden reflejar el paso transplacentario del fármaco en lugar de su ingesta a través de la leche materna (19).

2. Relación de concentración del fármaco entre la leche y el plasma materno (Cociente L/P). Es una estimación de la distribución del fármaco entre el suero materno y la leche. Se calcula dividiendo la concentración del fármaco en la leche materna por la concentración en el suero de la madre. El método actualmente aceptado para calcular la relación L/P es utilizar la relación entre el área bajo la curva (AUC) de la leche y el suero. El cálculo del AUC a partir de la recolección de varias muestras (cinco o seis) de fármaco en estado estacionario durante un intervalo de tiempo específico es probablemente el método más adecuado (15). Una relación L/P <1 es un buen indicador de que sólo se transfieren niveles mínimos del fármaco a la leche, mientras que una relación >1,5 implica que niveles elevados del fármaco pueden ser secuestrados en la leche (15). Desde una perspectiva clínica, la relación L/P no predice la seguridad de un fármaco para el lactante durante la lactancia (15).

3. Dosis relativa para el lactante (DRL**).** Se calcula dividiendo la dosis del lactante a través de la leche en mg/kg/día por la dosis materna en mg/kg/día. Este método de normalización del peso indica aproximadamente qué cantidad de dosis materna está recibiendo el lactante. Se han propuesto varios puntos de corte para este índice (20). Se considera aceptable una DRL <10 % del extremo más bajo de la dosis materna ajustada al peso para los lactantes, y se deben evitar DRL >25 % en madres lactantes. Recientemente, un grupo de trabajo en Dinamarca desarrolló directrices para el uso de drogas psicotrópicas durante la lactancia materna que utilizaron un límite igualmente arbitrario, pero más conservador, del 5% como límite de aceptabilidad de la lactancia materna (21). Aunque la DRL se acepta como una medida de seguridad de la medicación durante la lactancia, tiene algunas limitaciones. Por ejemplo, si aumenta la dosis del medicamento administrado a la madre, también aumenta la dosis que el bebé recibe a través de la leche materna, pero la DRL generalmente no cambia. Por lo tanto, la DRL no es fiable para representar la seguridad del medicamento durante la lactancia para un medicamento con un amplio rango de dosificación, especialmente aquellos con una DRL cerca del punto de corte

del 10%. Otra limitación es que la DRL no tiene en cuenta la posibilidad de diferencias en la biodisponibilidad del fármaco en relación con la edad del lactante (22).

4. Relación de concentración de fármaco entre suero infantil y suero materno (Cociente I/P). Es la concentración del fármaco en el suero de la lactante dividida por la concentración en el suero de la madre. La comparación de la concentración sérica es atractiva porque minimiza variables como la biodisponibilidad y las diferencias en el aclaramiento entre el lactante y la madre. Es más preciso cuando se aplica en estado estacionario a fármacos que tienen una vida media de eliminación relativamente larga porque los niveles maternos e infantiles no fluctúan sustancialmente. Cuando se obtienen muestras en estas condiciones, probablemente sería suficiente una medición fiable de muestras de sangre de la madre y el bebé, aunque esta posibilidad no se ha probado rigurosamente. Para los fármacos con una vida media de eliminación corta, se requieren múltiples muestras de plasma para obtener concentraciones séricas promedio o mediciones de AUC para obtener una relación I/P fiable (22). Al igual que con la DRL, la Academia Estadounidense de Pediatría consideró aceptable un fármaco que produce una relación I/P en estado estacionario inferior al 10% del extremo más bajo del rango de concentración terapéutica, y una relación superior al 25% se consideró inaceptable (23). Puede ocurrir un problema con la relación I/P en relación con el momento de la toma de muestras del lactante si la madre estaba tomando el medicamento durante el embarazo. En general, se pasa una cantidad mucho mayor del fármaco al feto por vía transplacentaria que al lactante a través de la leche materna. Por lo tanto, la obtención de muestras de sangre infantil demasiado pronto después del parto (<7 días) puede reflejar un paso transplacentario en lugar de una transferencia de leche materna (19).

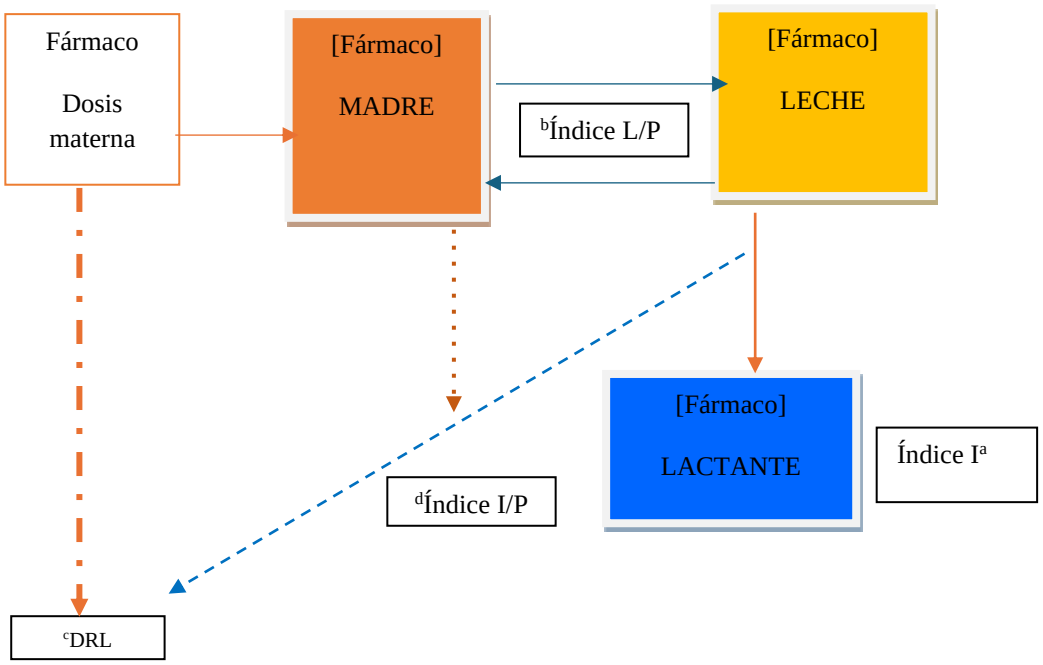
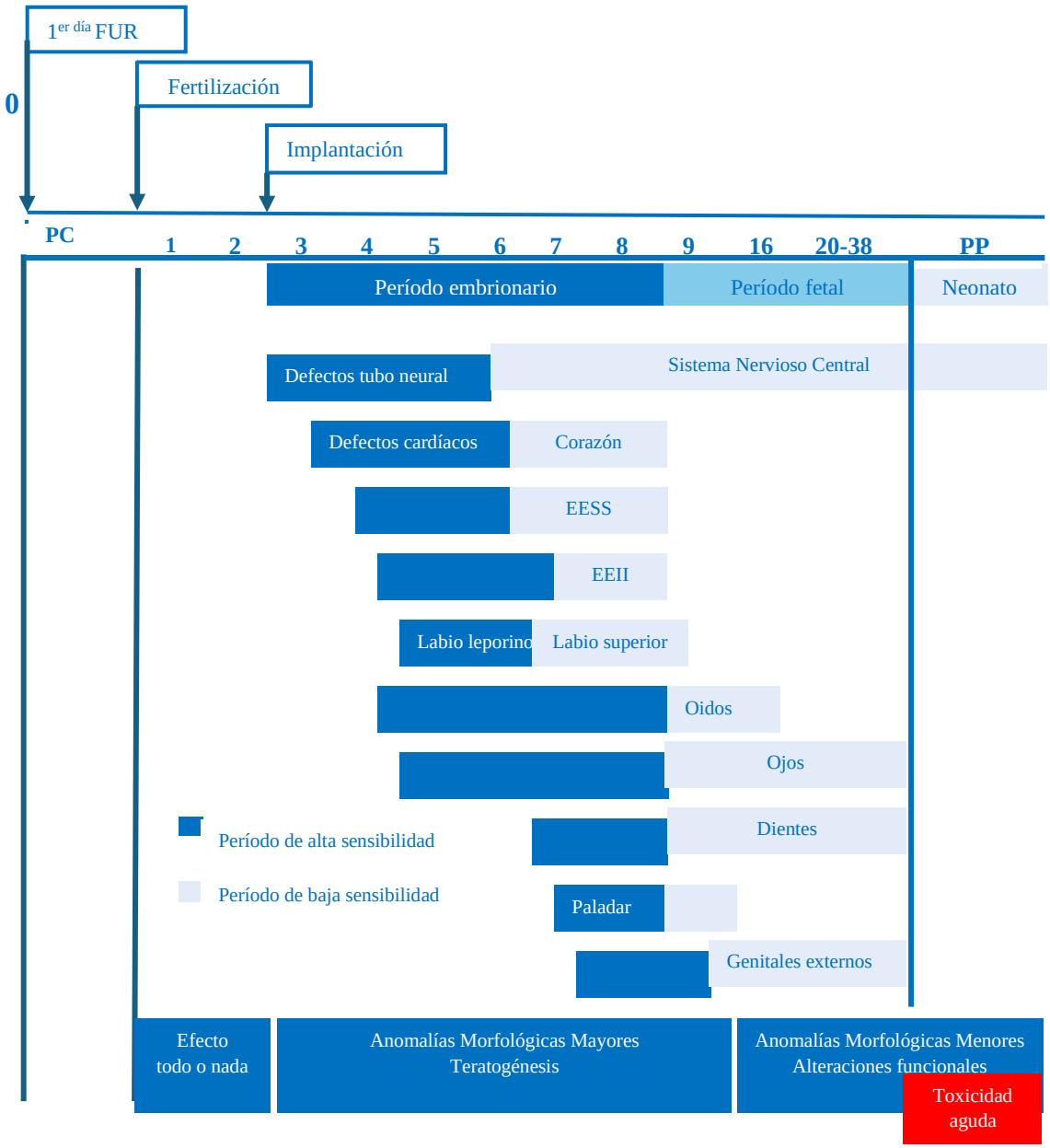


Figura 2. Métodos de estimación de la trasferencia de fármacos en la unidad madre-leche-lactante. Método de estimación directa: [a]índice I=concentración de fármaco en el suero infantil (I). Métodos de estimación indirecta:[b] índice L/P=cociente de concentración del fármaco entre la leche y el suero materno; [c]DRL=dosis relativa para el lactante; [d]Índice I/P=cociente de concentración de fármaco entre suero infantil y suero materno. Figura creada por la autora.

5.1.2 Riesgos fetales y neonatales asociados a la exposición prenatal a fármaco

El efecto de un fármaco sobre el feto depende en gran medida de la edad fetal en el momento de la exposición, de la permeabilidad placentaria, de los factores maternos y de la potencia del fármaco. Describimos a continuación los riesgos asociados a la exposición prenatal a fármacos (teratogénesis, complicaciones obstétricas, complicaciones neonatales agudas y del neurodesarrollo). **Figura 3.**



Abreviaturas: AM= anomalía morfológica; EEII= extremidades inferiores; EESS=extremidades superiores; FUR=fecha de última regla; PC= preconcepcional; PP=posparto

Figura 3. Riesgos fetales y neonatales. Período crítico en el desarrollo embrionario y fetal para originar malformaciones congénitas. Figura creada por la autora.

5.1.2.1 Desarrollo fetal y teratogénesis

Se considera teratogénico a cualquier agente que interfiera en el proceso de desarrollo uterino y que produzca algún tipo de malformación o disfunción congénita. La frecuencia de malformaciones en la población general se ha estimado en un 2-3% para las malformaciones congénitas mayores y en un 7-10% para las menores. El riesgo de malformación tras la exposición fetal a un fármaco debe ser siempre comparado con estas cifras de población general. El 40 % de las malformaciones congénitas son de origen

desconocido y entre un 12-25% son de etiología genética. Un 20% son debidas a la interacción entre factores hereditarios y ambientales. Entre un 5-9% de las malformaciones son atribuibles a factores ambientales como agente único (p. ej infección materna como la rubeola, enfermedad materna crónica como diabetes o la epilepsia, o productos químicos o fármacos). La exposición a fármacos se considera responsable de un 2-3% de estas anomalías (24).

El período teratogénico abarca desde el día 31 tras la fecha de última regla (FUR) hasta 71 días de este último período menstrual. Consta de varias etapas:

1. Etapa preimplantacional. Corresponde a la primera semana pos-fertilización. Es el período de máxima embriotoxicidad. Durante la formación de la blástula las células son totipotenciales y si algunas son lesionadas, se inician fenómenos de reparación o de reemplazo celular. En esta etapa, la exposición a un agente teratogénico tiene un efecto de "todo o nada": o se afecta totalmente (lo que, generalmente, da lugar a un aborto que muchas veces pasa inadvertido para la mujer, ya que ni siquiera sabe que está embarazada) o no hay lesión.

2. Etapa de embriogénesis. Entre los días 20 y 56 pos-fertilización. El embrión es vulnerable y se pueden producir malformaciones organoespecíficas (anomalías del tubo neural, malformaciones cardiacas y faciales), dando lugar en muchos casos a abortos o malformaciones fetales incompatibles con la vida extrauterina.

3. Etapa fetal. A partir del día 56 pos-fertilización. La sensibilidad a las malformaciones se reduce de forma significativa. Los acontecimientos más importantes son el cierre completo del paladar, la reducción de la hernia umbilical al final de la novena semana, la diferenciación de los genitales externos y la histogénesis del sistema nervioso central (SNC). Este último proceso dura todo el período de desarrollo intrauterino y no se completa hasta meses después del nacimiento. Se pueden producir alteraciones en el crecimiento y desarrollo funcional del feto o alteraciones morfológicas que generalmente son de menor gravedad que las ocasionadas en la etapa de embriogénesis.

5.1.2.2 Complicaciones obstétricas

Las complicaciones obstétricas asociadas a la exposición intrauterina a fármacos incluyen la infertilidad, el aborto, la diabetes gestacional, el polihidramnios, la hipertensión gestacional, la preeclampsia, el parto pretérmino (menos de 37 semanas de gestación) y el parto distócico. Ver **Glosario.**

5.1.2.3 Complicaciones neonatales y del neurodesarrollo

Las complicaciones neonatales asociadas a la exposición intrauterina a fármacos incluyen complicaciones neonatales agudas tales como el bajo peso al nacer, el bajo peso para la edad gestacional, la macrosomía, el sufrimiento fetal agudo (SFA) así un test de Apgar alterado. La teratogenia neurocomportamental hace referencia a los potenciales efectos neuroconductuales tras la exposición a fármacos intraútero. La migración y la diferenciación neuronal ocurren durante la vida intrauterina y continúan durante los primeros años de vida, por lo que el sistema nervioso central resulta especialmente vulnerable a los potenciales efectos adversos de los fármacos. Ver **Glosario.**

5.1.3 Categorías de riesgo utilizadas para los fármacos durante el embarazo y la lactancia.

Una de las consecuencias de la tragedia de la talidomida en la década de 1960, además de las relativas a la normativa sobre ensayos preclínicos, fue el surgimiento de la necesidad de desarrollar una categorización de los medicamentos en cuanto al riesgo que suponen para el feto. Esta necesidad llevó a la introducción progresiva de diferentes categorías de riesgo para el embarazo en los diferentes países basadas en la evaluación de la información científica disponible.

La primera categoría de riesgo con respecto al uso de medicamentos durante el embarazo se desarrolló e introdujo en Suecia en 1978, denominada Catálogo sueco de medicamentos aprobados (Swedish Catalogue of Approved Drugs, FASS) y proponía cuatro categorías de riesgo (A, B, C, D). La categoría A correspondía al medicamento más seguro, y el posible posible riesgo del medicamento aumentaba gradualmente de A a D (25).

Sin embargo, las directrices más conocidas y aplicadas internacionalmente son las de la Administración de Alimentos y Medicamentos de Estados Unidos (Food and Drug Administration por sus siglas en inglés, FDA), que estableció por primera vez en 1979 un sistema de clasificación basado en los datos derivados de estudios en animales, en estudios no controlados y en estudios de vigilancia poscomercialización, según el cual los fármacos se dividían en 5 categorías (A, B, C, D, X) que estimaban el riesgo de toxicidad fetal. Ver **Tabla 2.** Las categorías de la FDA tenían como objetivo guiar la elección de medicamentos antes de la exposición fetal, en lugar de proporcionar información sobre cómo controlar el embarazo después de la exposición (26). Los críticos de la clasificación de la FDA señalaron que, aunque el sistema era fácil de usar, podría simplificar demasiado la complejidad de sopesar los riesgos para el feto frente a la necesidad de controlar adecuadamente las condiciones médicas maternas (27).

Tabla 2. Categorización de la FDA de EE. UU. sobre el riesgo de uso de drogas durante el embarazo: definiciones y estrategias de manejo[a].

Categoría	Definición	Estrategias de manejo
A	Los estudios controlados realizados en mujeres embarazadas no han demostrado un aumento en el riesgo de anormalidades fetales en ningún trimestre del embarazo.	Pueden prescribirse en cualquier trimestre del embarazo, ya que la posibilidad de daño fetal parece remota.
B	Los estudios realizados en animales no han demostrado riesgo fetal. No no hay estudios adecuados, ni bien controlados, en embarazadas; o bien los estudios en animales han mostrado un efecto adverso, pero los estudios realizados en mujeres embarazadas no han podido demostrar riesgo sobre el feto en ningún trimestre del embarazo.	El uso de estos medicamentos se acepta, generalmente, durante el embarazo.
C	Los estudios realizados en animales han demostrado efectos adversos en el feto. No hay estudios adecuados, ni bien controlados, en mujeres embarazadas, o bien no se han realizado estudios en animales, ni existen estudios adecuados y bien controlados en embarazadas.	Estos medicamentos deben ser administrados solamente si el posible beneficio deseado justifica el riesgo potencial en el feto.
D	Los estudios controlados y observacionales realizados en embarazadas han demostrado un riesgo para el feto.	El beneficio de su uso en mujeres embarazadas puede aceptarse a pesar del riesgo. Por ejemplo, si la vida del paciente está en riesgo o en enfermedades graves para las cuales los medicamentos más seguros no pueden usarse o son inefectivos.
X	Los estudios controlados y observacionales realizados en animales o en mujeres embarazadas han demostrado una clara evidencia de anormalidades o riesgo para el feto. El riesgo de la utilización del medicamento en la embarazada sobrepasa claramente cualquier posible beneficio.	El medicamento está contraindicado en la mujer que está o que puede quedar embarazada.

Abreviaturas; FDA=Food and Drug Administration

[a]A partir del 30 de junio de 2015 todos los medicamentos nuevos enviados para aprobación por la FDA, deben informar del riesgo teratogénico siguiendo las nuevas directrices.PLLR. Aquellos aprobados entre el 30 de junio de 2001 y el 29 de junio de 2015 deben ir adaptándose gradualmente al nuevo sistema, mientras que los aprobados antes del 30 de junio de 2001 no están sujetos a las nuevas normas. De todas formas, y para todos los medicamentos, la letra de la categoría de riesgo teratogénico debe ser retirada de manera definitiva el 29 de junio de 2018.

Tabla adaptada de Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Baltimore: Williams & Wilkins; 1998 (28).

En 2015, la FDA reemplazó las antiguas categorías por un formato de etiquetado conocido como Regla Final de Etiquetado de Embarazo y Lactancia (Pregnancy and Lactation Labeling Final Rule por sus siglas en inglés, PLLR), más similar a la normativa europea. Consta de secciones y subsecciones narrativas: “Embarazo, Lactancia y Mujeres y Hombres con potencial reproductivo”. La subsección sobre “Embarazo” contiene un

registro que recopila datos sobre mujeres embarazadas y señala cualquier riesgo potencial del uso de medicamentos para la madre y el feto en desarrollo. La subsección sobre "Lactancia" contiene información sobre el momento de la lactancia, la excreción de medicamentos en la leche materna y los riesgos para el lactante. Finalmente, la subsección "Mujeres y Hombres con potencial reproductivo" incluye información clínica relevante y recomendaciones sobre fertilidad, aborto espontáneo, anticoncepción y pruebas de embarazo (29).

La EMA publicó en 2008 las pautas de recomendación para la evaluación de medicamentos en la reproducción humana y el riesgo en el embarazo y la lactancia que pueden consultarse en su página web (http://www.ema.europa./eu/ema/). Esta agencia establece en su Guía de Buena Práctica en Farmacovigilancia para poblaciones específicas "mujeres embarazadas y lactantes" que es necesario realizar estudios observacionales post autorización de seguridad en los fármacos que no puedan ser discontinuados durante el embarazo, fármacos para tratar las enfermedades propias de la gestación/lactancia o los que en estudios preclínicos han mostrado algún tipo de riesgo para la descendencia (18). En España, las autorizaciones, así como las recomendaciones de uso de medicamentos dependen de la Agencia Española del Medicamento (AEMPS) en coordinación con la Agencia Europea de Medicamentos (EMA) (18).

En lo que respecta a la utilización de fármacos durante la lactancia materna, una de las clasificaciones internacionales más utilizadas es la creada por el farmacólogo, Dr Thomas Hale (19). Este recurso se sustenta en los estudios basados en evidencia más recientes para evaluar la transferencia de fármacos de uso común de la madre a la leche humana y el riesgo relativo de los fármacos, incluidos en las categorías de riesgo de lactancia (LRC). Las categorías de riesgo están marcadas con las letras y números L1, L2, L3, L4 y L5, y representan desde la seguridad del fármaco para emplearse durante la lactancia hasta los que están totalmente contraindicados, en ese orden (19). Ver **Tabla 3**.

En un reciente estudio, Kapell y cols. (2023) (30), en el que se compararon las secciones de etiquetado sobre embarazo y lactancia de 31 medicamentos aprobados y se evaluaron las tendencias en cuanto al uso de la concordancia y discordancia del lenguaje relacionado con el uso durante el embarazo y la lactancia, la EMA y la FDA, tuvieron

una alta discordancia entre el lenguaje de las etiquetas sobre embarazo y lactancia, en el 68% y el 71% de las etiquetas, respectivamente. Solo el 10% de las etiquetas sobre el embarazo y el 16% de las etiquetas sobre la lactancia incluyen datos en humanos. Este estudio destaca la necesidad de avanzar en la recopilación de datos y la inclusión de personas embarazadas y lactantes en ensayos clínicos para informar las prácticas de prescripción y optimizar la atención clínica (30).

Tabla 3. Categorías farmacológicas de riesgo en la lactancia según el Dr. Hale[a].

Categoria	Definición	Estrategia de manejo
L1	Fármaco que ha sido tomado por un gran número de madres que amamantan sin observarse ningún incremento en los efectos adversos en el lactante. Los estudios controlados en mujeres que amamantan no demuestran un riesgo para el lactante, y la posibilidad de daño al lactante es remota o el producto no es biodisponible por vía oral en un lactante.	Máxima seguidad
L2	Fármaco que se ha estudiado en un número limitado de mujeres que amamantan y que no se ha observado un incremento de los efectos adversos en el lactante y/o la evidencia de un riesgo probable demostrado que siga al uso de este medicamento en una mujer que amamanta es remota.	Seguro
L3	No hay estudios controlados en mujeres que amamantan; sin embargo, el riesgo de efectos adversos para un lactante es posible o los estudios controlados muestran solo efectos adversos mínimos no amenazantes. Se deben administrar el fármaco solo si el beneficio potencial justifica el riesgo potencial para el lactante.	Moderadamente seguro
L4	Existe evidencia positiva de riesgo para un lactante que es amamantado, o para la producción de leche materna, pero los beneficios del uso en madres que amamantan pueden ser aceptables a pesar del riesgo para el lactante (p.ej.: si el fármaco es necesario en una situación potencialmente mortal o enfermedad grave para la cual no se puedan utilizar medicamentos seguros o no son efectivos).	Posiblemente peligroso
L5	Los estudios en madres que amamantan han demostrado que existe un riesgo significativo y documentado para el neonato/lactante basado en la experiencia humana; o es un fármaco que tiene un alto riesgo de causar un daño significativo a un neonato/lactante. El riesgo de usar el fármaco en mujeres que amamantan claramente supera cualquier posible beneficio de la lactancia materna.	Contraindicado

[a]Tabla adaptada de Hale TW, Rowe HE. Medications & mothers' milk 2017: Hale, Thomas W., Rowe, Hilary E (19)

5.2 TRASTORNO BIPOLAR

5.2.1 Definición y epidemiología

El trastorno bipolar (TB) es un trastorno crónico recurrente caracterizado por fluctuaciones en el estado de ánimo (episodios de depresión que se alternan con episodios de hipomanía y/o manía, y episodios mixtos) separados por períodos de estado de ánimo y funcionamiento relativamente normales (31). La prevalencia de TB en la población general es de alrededor del 2% al 3%, independientemente de su origen étnico, nacionalidad, o nivel socioeconómico. Comparado con otros trastornos mentales, es uno de los trastornos psiquiátricos más hereditarios, con una tasa de heredabilidad de alrededor del 60-85% (32). Es una enfermedad poligénica con una superposición genética sustancial con otras enfermedades mentales (33). Factores ambientales, como eventos estresantes de la vida, particularmente los abusos sexuales y físicos, así como el maltrato emocional, se han asociado no sólo con la aparición de TB, sino también con el curso de la enfermedad (34). La Organización Mundial de la Salud considera que es la 6ª causa de discapacidad a nivel mundial ya que pueden provocar deterioro cognitivo y funcional y un aumento de la mortalidad, en particular por suicidio y enfermedades cardiovasculares (35).

Típicamente, el TB se manifiesta durante la adolescencia tardía o la edad adulta temprana, y a menudo comienza antes de los 25 años (36). El TB BD I tiene una prevalencia similar entre hombres y mujeres, mientras que TB II es más frecuente en mujeres (37). No se han encontrado diferencias consistentes de sexo en una serie de variables, incluidas las tasas de episodios depresivos, la edad y la polaridad de inicio, los síntomas, la gravedad de la enfermedad, la respuesta al tratamiento y la conducta suicida. Sin embargo, la principal distinción entre hombres y mujeres con trastorno bipolar es el impacto que los acontecimientos de la vida reproductiva, en particular el parto, tienen en las mujeres con TB (38).

5.2.2 Tipos de episodios afectivos

El diagnóstico temprano del TB es difícil en la práctica clínica, ya que la aparición del trastorno bipolar se caracteriza comúnmente por síntomas inespecíficos, labilidad del estado de ánimo o un episodio depresivo, que puede ser similar en presentación a la depresión unipolar. La detección de episodios hipomaníacos y la evaluación clínica longitudinal son fundamentales para diferenciar el trastorno bipolar de otros trastornos del ánimo.

El trastorno bipolar se caracteriza por episodios de manía, hipomanía y depresión que afectan significativamente el funcionamiento sociolaboral (31):

1. Episodio maníaco: se caracteriza por un estado de ánimo elevado y anormalmente optimista, un comportamiento expansivo, cambios del estado de ánimo bruscos (puede pasar de la euforia a la ira en cuestión de segundos), distraibilidad, aumento de la autoestima, aumento del impulso motor y una reducción de la necesidad de dormir (39). Estos síntomas deben estar presentes la mayor parte del día, casi todos los días durante al menos una semana, o menos si es necesaria la hospitalizado (40). Los síntomas psicóticos (delirios o alucinaciones) están presentes en aproximadamente el 75% de los pacientes que presentan un episodio maníaco agudo (40) y puede ser congruentes con el estado de ánimo (p.ej., grandiosidad, ideación megalomaniaca o místico-religiosa) o incongruentes (p.ej., autorreferencialidad, temple interpretativo, ideas de perjuicio y/o persecución) (40).

2. Episodio hipomaníaco: es una forma más leve y breve de manía, no se acompaña de síntomas psicóticos, no requiere tratamiento en régimen de hospitalización y su impacto sociolaboral comparado con la manía es menor. El diagnóstico de hipomanía requiere la presencia de síntomas afectivos durante al menos cuatro días consecutivos (40).

3. Episodio depresivo: se caracteriza por un estado de ánimo deprimido (p.ej., sentimientos de tristeza, vacio o desesperanza, irritabilidad), pérdida de interés o de placer por todas o casi todas las actividades la mayor parte del día, dificultad para tomar decisiones, distraibilidad, sentimientos de inutilidad o culpabilidad excesiva (que puede llegar a ser delirantes), fatiga o pérdida de energía, retraso psicotomor o agitación, insomnio o hipersomnia, pérdida o ganancia ponderal, aislamiento social, entre otros, durante al menos durante dos semanas (40). Los síntomas se asocian con un deterioro funcional significativo, una calidad de vida reducida, comorbilidades somáticas y conducta suicida. En concreto, la depresión bipolar se caracteriza típicamente por hipersomnia, inhibición psicomotora, labilidad emocional y apatía (41).

4. Episodio mixto: se caracteriza por la presencia de síntomas tanto depresivos como maníacos simultáneamente. El manual de diagnóstico de trastornos mentales, en su 5ª Edición (DSM-5) (2013) (40). reemplazó la categoría "episodio mixto" por el especificador "con características mixtas", que exige la presencia de tres o más síntomas de la polaridad opuesta y elimina los síntomas superpuestos, es decir, aquellos que pueden estar presentes tanto en la depresión como en la manía, como son la distrabilidad, la irritabilidad y la agitación psicomotora. El episodio mixto se ha asociado con un pronóstico más severo, un mayor número de episodios, un mayor número de muertes por suicidio y comorbilidades (39).

5.2.3 Clasificación diagnóstica del trastorno bipolar

El DSM-5 (40) clasifica el trastorno bipolar en subtipos: bipolar I, bipolar II, ciclotimia, trastornos bipolares inducidos por sustancias o debidos a una afección médica general, y otros trastornos bipolares y relacionados específicos:

1. Trastorno bipolar I (TB I): requiere al menos la presencia un episodio de manía, actual o previo, mientras que no es necesario tener antecedentes de episodios hipomaníacos y depresivos para establecer este diagnóstico. Sin embargo, a lo largo del curso de la enfermedad, la mayoría de los pacientes generalmente

experimentan episodios hipomaníacos y depresivos mayores además de episodios maníacos (39,40).

2. Trastorno bipolar II (TB II): requiere un episodio de hipomanía además de un episodio de depresión mayor. Típicamente incluye individuos con antecedentes de episodios depresivos que alternan con uno o más episodios hipomaníacos, sin antecedentes de episodios maníacos (39,40). Comparado con los pacientes con TB I, los pacientes con TB II generalmente sufren de mayores tasas de recurrencia y proporción de tiempo en depresión y períodos más cortos de eutimia (41).

1. Ciclotimia: consiste en la alternancia, durante más de dos años y sin largos períodos de estabilidad (< 2 meses), entre episodios de síntomas hipomaníacos y de síntomas depresivos sin que lleguen a cumplir criterios de depresión mayor, episodio maníaco ni episodio hipomaníaco (39, 40).

2. Trastorno bipolar inducido por sustancias/medicamentos: se define por la presencia de un trastorno del estado de ánimo compatible con manía que se desarrolla durante o poco después de una exposición, intoxicación o abstinencia de una sustancia (p. ej., cocaína, corticosteroides) y que es capaz de producir los síntomas mencionados (39, 40).

3. Trastorno bipolar y trastorno relacionado debido a otra afección médica: se define por la presencia de una alteración del estado de ánimo compatible con manía causada por una enfermedad (p. ej., síndrome de Cushing, traumatismo encefalocraneal), que no se produce exclusivamente durante un episodio de confusión (39, 40).

4. Trastorno bipolar no especificado: se define como un trastorno con características bipolares claras que no cumplen criterios específicos para otros trastornos bipolares (39, 40).

Por otra parte, el especificador de" inicio periparto" se puede aplicar al episodio de estado de ánimo más reciente si el inicio comenzó durante el embarazo o dentro de las

4 semanas posteriores al parto, aunque algunos grupos de investigadores abogan por una extensión de hasta 1 año basándose en factores psicosociales. (40).

5.2.4 Trastorno bipolar en la mujer en la etapa reproductiva

Las mujeres con trastorno bipolar son más propensas a presentar un TB tipo II (alternancia de episodios de depresión e hipomanía), ciclación rápida (≥ 4 episodios / año), episodios mixtos y comorbilidad médica (ej.: enfermedad tiroidea, migraña, obesidad) y psiquiátrica (ej.: ansiedad) (42).

En la etapa perinatal, que comprende el embarazo y el primer año posparto, las mujeres pueden tener un mayor riesgo de sufrir episodios del estado de ánimo del espectro bipolar. Las razones son multifactoriales e incluyen: la superposición entre los años reproductivos máximos y la edad de inicio del trastorno bipolar, los cambios hormonales y fisiológicos que acompañan al embarazo, y el estrés relacionado con el parto y la crianza de los hijos (43). En las adolescentes, el trastorno bipolar se asocia con un riesgo 20 veces mayor de embarazo temprano y un riesgo 25 veces mayor de embarazo temprano repetido, incluso después de ajustar por factores de confusión (44).

Las mujeres con trastorno bipolar tienen un alto riesgo de recaída de los síntomas durante la etapa perinatal (45, 46). Investigaciones recientes indican un riesgo de recurrencia del trastorno bipolar durante el embarazo, con tasas que oscilan entre el 4% y el 73% (43, 47). Una revisión sistemática encontró que las personas embarazadas con trastorno bipolar tienen más probabilidades de experimentar episodios depresivos o mixtos que episodios hipomaníacos o maníacos (48). Existe evidencia consistente de altas tasas tanto de aparición inicial como de recurrencia del trastorno bipolar en el período posparto (49). En un metanálisis de más de 3000 pacientes diagnosticadas con trastorno bipolar, la tasa de recurrencia posparto fue del 35% (47). Otro estudio informó que el 30% de las mujeres embarazadas diagnosticadas con trastorno bipolar experimentaron un episodio posparto (50). Un historial de trastorno bipolar está relacionado con un mayor riesgo de hospitalización psiquiátrica en el posparto (45). El período posparto inmediato

es un momento crítico de mayor riesgo tanto de manía como de psicosis, y la mayoría de los episodios ocurren dentro de las 4 a 6 semanas posteriores al nacimiento (45). Además, el TB es un factor de riesgo de suicidio perinatal, psicosis posparto e infanticidio (51). Por otra parte, el trastorno bipolar se ha asociado con un ligero incremento del riesgo para las complicaciones obstétricas (diabetes gestacional, hipertensión, partos prematuros y cesáreas) y neonatales (recién nacidos pequeños o grandes para la edad gestacional) (52, 53, 54).

5.2.4.1 Manejo del trastorno bipolar perinatal

Los objetivos del tratamiento del TB en la etapa perinatal son mantener el bienestar materno, garantizar la seguridad fetal y prepararse para el período posparto. Las recurrencias de los trastornos bipolares impactan en la salud y el bienestar materno-fetal lo que justifica la utilización de los tratamientos farmacológicos (55). Dependiendo del estado de la enfermedad, las recomendaciones sobre su manejo varían. En las fases de descompensación aguda (depresión, episodios mixtos, manía o hipomanía) el tratamiento se centra en la remisión del episodio índice, mientras que en las fases de eutimia el tratamiento tiene como objetivo la prevención de futuras recaídas (39). El mantenimiento del tratamiento con estabilizadores de ánimo solos o en combinación durante la gestación y el posparto es efectivo en la prevención de recurrencias (47), mientras que la discontinuación de los tratamientos eutimizantes, sobre todo si se realiza de manera rápida (< 15 días) se asocia con recaídas más tempranas durante el embarazo (56). La seguridad de los psicofármacos utilizados para el tratamiento del TB durante la etapa perinatal debe considerarse en términos del potencial riesgo teratogénico asociado, de los resultados obstétricos y neonatales, así como de los efectos neuroconductuales a largo plazo. Un punto importante en la interpretación de los datos sobre la seguridad de los psicofármacos es que los datos deben considerarse en el contexto de las tasas iniciales de malformaciones congénitas (2 a 3,5 %) en estudios de población general (24). Además, las pacientes con TB pueden presentar un riesgo ligeramente mayor de resultados adversos en el embarazo no solo debido a la exposición a los psicofármacos, sino también potencialmente a factores del estilo de vida, obesidad o comorbilidades frecuentemente asociadas (que actúan como factores de confusión en los estudios) (42, 52, 53, 54).

La **Tabla 4** incluye una breve descripción de los tratamientos farmacológicos y biológicos no farmacológicos comúnmente utilizados en el manejo del TB y sus indicaciones de tratamiento, así como información sobre seguridad reproductiva en el embarazo y la lactancia y recomendaciones de manejo clínico en la etapa perinatal (57-67). Si bien los estabilizadores del estado de ánimo son uno de los tratamientos más eficaces para las fases agudas y la prevención a largo plazo de las recaídas del TB, el ácido valproico (AVP) no se considera un fármaco de primera línea en la etapa perinatal por su riesgo teratogénico (aproximadamente 10% de malformaciones congénitas tras exposición en el primer trimestre de embarazo) y su asociación con con alteraciones en el neurodesarrollo a largo plazo de los fetos expuestos intraútero. En Europa, la Agencia Europea del Medicamento contraindica el uso de AVP durante el embarazo en el TB en todos los casos y en la epilepsia, salvo que no exista una alternativa (59, 60). La carbamazepina también se ha asociado con un riesgo ligeramente de malformaciones congénitas (3-6%) y se desaconseja su uso en el embarazo (67, 68). La terapia electroconvulsiva, la estimulación magnética transcraneal y la fototerapia son opciones de tratamiento que no presentan riesgos perinatales significativos y pueden estar infrautilizadas (69, 70, 71).

Además, son necesarias estrategias psicosociales (psicoeducación para mantener un estilo de vida saludable y preservar el descanso nocturno, incremento del apoyo social, reducción del estrés parental) y estrategias psicoterápicas (terapia cognitivo conductual, terapia familiar y terapia interpersonal) basadas en la evidencia para un óptimo tratamiento de estas pacientes (39, 67).

Tabla 4.1. Seguridad reproductiva y recomendaciones de manejo en el embarazo y la lactancia de los psicofármacos y tratamientos biológicos comúnmente utilizados en el tratamiento del trastorno bipolar.

Fármaco	Indicaciones de uso en el TB			Seguridad reproductiva y recomendaciones de manejo en el embarazo y la lactancia			
	Mania	Depresión	Mantenimiento	Riesgos fetales/neonatales potenciales	Recomendaciones clínicas	Riesgo Embarazo[a]	Riesgo Lactancia[b] DRL Observación
Litio (Li)	+++	++	+++	Riesgo de anomalía de Ebstein tras exposición en TM1 (0,1%-0,05%) Dosis de litio > 900 mg/día se asocian con incremento del riesgo teratogénico Incremento del aclaramiento renal de Li	Suplementación maternal con ac. fólico 5mg/d Ecocardiografia fetal sem 16-18 Obtener [Li] basal preconcepcional Monitorizar [Li] y ajuste de dosis así como function renal y tiroidea	D	L4 DRL 0,87%-7,29 % Monitorización clínica pediátrica
Ácido valproico (AVP)	+++	+	++	Riesgo de malformaciones congénitas mayores incrementado (10%) tras exposición TM1 Secuelas neuroconductuales significativas en fetos expuestos intraútero	No recomendado en niñas y mujeres en edad reproductiva. Informar de los riesgos teratogénicos. Anticoncepción efectiva Suplementación con ac. fólico 5 mg/d Usar a la dosis mímica efectiva < 750 mg/d A-fetoproteina sem 15 Ecocardiografia fetal sem16-18	D	L4 DRL 0,9%-5,6% Monitorización clínica pediátrica
Carbamazepina (CBZ)	+++	+	++	Riesgo de malformaciones congénitas mayores tras exposición TM1(3%-6%) Dosis recomendada < 1000 mg/día Riesgo de hemorragia neonatal por deficiencia de Vit K	Suplementación materna con ac. fólico 5 mg/d Monitorización [CBZ] opcional, no es preciso ajuste de dosis Suplementación neonatal con Vit K 1 mg	D	L2 DRL 3,8%-5,9% Monitorización clínica pediátrica
Lamotrigina (LTG)	– – –	++	+++	Riesgo de malformaciones congénitas mayores tras exposición TM1 en la mayoría de los estudios /(2-%-3%) es comparable a las tasas de población general Puede precisar ajuste de dosis por incremento de la matabolización hepática Sin secuelas neuroconductuales significativas en fetos expuestos intraútero	Suplementación maternal con ac. fólico 5 mg/d [LTG] basal preconcepcional. Monitorizar [LTG] y ajuste de dosis en embarazo 20%-25% para mantener concentraciones terapeúticas Reducir un 25% la dosis en el posparto inmediato, después cada 3-4 días hasta la dosis preconcepcional	C	L2 DRL 6,6%-18% Monitorización clínica pediátrica

Abreviaturas: DRL=dosis relativa del lactante ; TB=trastorno bipolar; TM1= primer trimestre de gestación

[a]Categorías de riesgo en el embarazo FDA: A = estudios controlados no muestran ningún riesgo; B = no hay evidencia de riesgo en humanos; C = no se puede descartar el riesgo; D = evidencia positiva de riesgo; X = contraindicado en el embarazo. [b]Categorias de riesgo para la lactancia: L1 = más segura; L2 = más seguro; L3 = moderadamente seguro; L4 = posiblemente peligroso; L5 = contraindicado.

Tabla adaptada de Grande y cols. (2015) (57); Anmella y cols. (2019) (58); AEMPS (2018) (59); EMA (2018) (60); Hasser y cols. (2024) (61); SingH y cols. (2022) (62); Boice y Buist (2016)(63); Betchers y cols. (2019) (64); Bertcher y cols. (2019) (65); AGOG (2007) (66); Vigo y cols. (2024) (67) y Vossler (2019) (68).

Tabla 4.2. Seguridad reproductiva y recomendaciones de manejo en el embarazo y la lactancia de los psicofármacos y tratamiento biológicos comúnmente utilizados en el tratamiento del trastorno bipolar.

Fármaco	Indicaciones de uso en el TB			Seguridad reproductiva y recomendaciones de manejo en el embarazo y la lactancia			
	Mania	Depresión	Mantenimiento	Riesgos fetales/neonatales potenciales	Recomendaciones clínicas	Riesgo Embarazo[a]	Riesgo Lactancia[b] DRL Observación
Aripiprazol (ARI)	+++	-	++	Riesgo de malformaciones congénitas mayores tras exposición TM1 alrededor del 3,5%. RIS se ha asociado con un ligero incremento en el riesgo pero necesita ser replicado. Puede incrementar el riesgo de diabetes gestacional. Hiperprolactinemia por RIS que dificulte la concepción	Monitorización periodica de la ganancia poderal y la glucemia para OLZ y QTP. Realizar ecografia de control del crecimiento fetal al final del embarazo La sedación maternal puede impactar en la stomas de leche nocturna.	C	L3 / DRL 0,7%-6,4 %
Olanzapina (OLZ)	+++	+++	++			C	L2 / DRL 0,28%-2,24%
Quetiapina (QTP)	+++	+++	+++			C	L2 / DRL 3,8%-5,9%
Risperidona (RIS)	++	-	++			C	L2 / DRL 2,8%-9,1%
Clozapina (CLZ)	+	+	++	Datos limitados sobre seguridad reproductiva. Puede incrementar el riesgo de diabetes gestacional	Reducir dosis de clozapina si la gestante reduce o suspende el consume de tabaco Monitorización del lactante expuesto intrautero a CLZ por riesgo de agranulocitosis	B	L3 / DRL 1,3%-1,4%
Antidepresivos ISRS Fuoxetina(FLU) Es/Citalopram (S/CIT) Sertralina(SER) Paroxetina (PRX) Fluvoxamina (FVX)	- -	+	+	PRX: Pequeño incremento del riesgo de malformaciones congénitas cardiaacas tras exposición en TM1(2/1000 nacimientos) PRX / FLU: Controversia sobre riesgo de HTP tras exposición en TM3 Adaptación neonatal: 1/3 de los fetos expuestos TM3	Realizar ecocardiograma fetal si exposición TM1 a PRX	C D PRX	L2 DRL: FLU 1,6%-14,6% S/CIT 3,5%-5,3% SER 0,4%-2,2% PRX 1,3%-2,5% FVX 0,3%-1,4%
TEC	++	++	+	Necesidad de anestesia general en el tratamiento con TEC	Monitorización ecográfica fetal y control obstétrico post-TEC	-	-
EMT	-	++	-				
Fototerapia	-	++	-				

Abreviaturas: DRL=dosis relativa del lactante; TB=trastorno bipolar; TM1= primer trimestre de gestación; TM3= tercer trimestre de gestación; TEC=terapia electroconvulsiva; EMT=estimulación magnética transcraneal

[a]Categorías de riesgo en el embarazo FDA: A = estudios controlados no muestran ningún riesgo; B = no hay evidencia de riesgo en humanos; C = no se puede descartar el riesgo; D = evidencia positiva de riesgo; X = contraindicado en el embarazo.

[b]Categorias de riesgo para la lactancia: L1 = más segura; L2 = más seguro; L3 = moderadamente seguro; L4 = posiblemente peligroso; L5 = contraindicado.

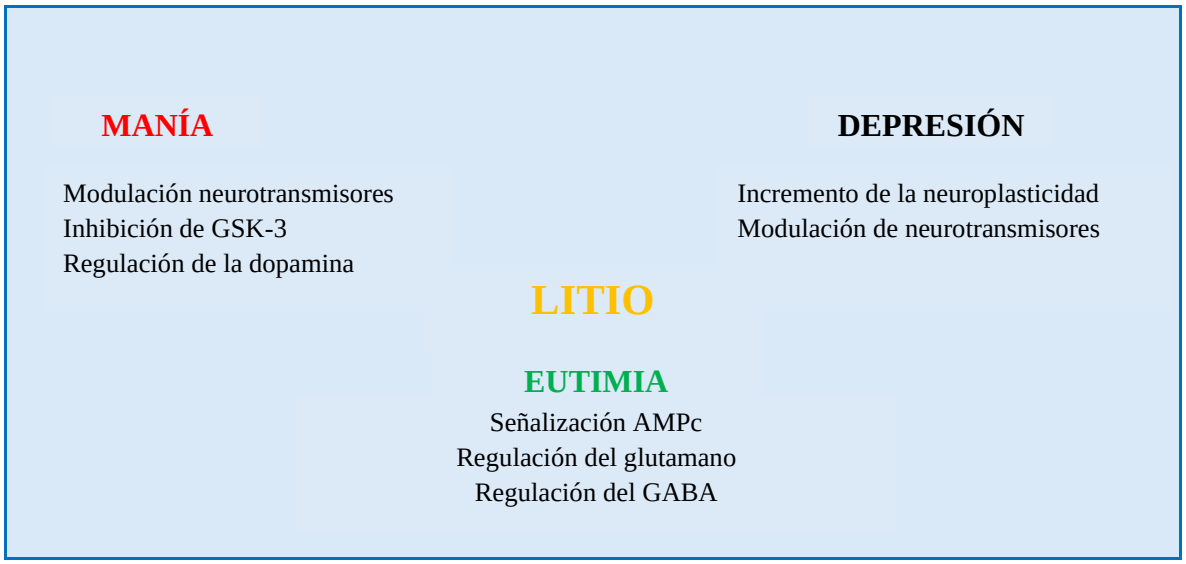
Tabla adaptada de Grande y cols. (2015) (57); Anmella y cols. (2019) (58); AEMPS (2018) (59); EMA (2018) (60); Hasser y cols. (2024) (61); SingH y cols. (2022) (62); Boice y Buist (2016)(63); Betchers y cols. (2019) (64); Bertcher y cols. (2019) (65); AGOG (2007) (66); Vigo y cols. (2024) (67) ; Vossler (2019) (68); Ward y cols. (2018) (69); Vigod y cols. (2019) (70) ; Bais y cols. (2016) (71).

5.3 EL LITIO ¿QUÉ ES Y COMO FUNCIONA?

El litio ($Li^{3+)}$ es el tercer elemento de la tabla periódica y es un catión monovalente que comparte ciertas propiedades con el sodio, el potasio y el calcio.

5.3.1 Propiedades farmacodinámicas del litio

El mecanismo de acción preciso del litio aún está bajo investigación y aún no se comprende completamente (72). El litio induce cambios en el transporte de sodio dentro de las células nerviosas y musculares y también influye en el metabolismo de los neurotransmisores, en particular las catecolaminas y la serotonina (73). El litio puede alterar la señalización intracelular a través de sistemas de segundos mensajeros al inhibir el monofosfato de inositol. Esta acción inhibidora impacta posteriormente en la neurotransmisión mediada por el sistema mensajero secundario fosfatidilinositol. Además, el litio disminuye la actividad de la proteína quinasa C, lo que provoca modificaciones en la expresión genómica asociadas con la neurotransmisión. El litio parece elevar las proteínas citoprotectoras, lo que potencialmente desencadena la neurogénesis y aumenta el volumen de sustancia gris (74, 75). Recientemente, se ha hecho hincapié en la inhibición del glicógeno sintetasa 3 quinasa (GSK-3b), en cambios a nivel de la homeoestasis de la plasticidad sináptica, y en la regulación de la expresión de microARN como mecanismos claves que podrían ayudar a entender el *gap* entre las funciones moleculares del litio y su eficacia clínica como estabilizador del ánimo (72). De modo que diferentes vías biológicas pueden verse afectadas durante los episodios afectivos. Ver **Figura 4.**



Abreviaturas. AMPc=Monofosfato de adenosina cíclico; GABA=Ácido gamma-aminobutírico; GSK-3=Glicógeno sintetasa 3 quinasa.

Figura 4. Mecanismo del litio en los episodios afectivos. Figura creada por la autora.

La respuesta clínica del litio como estabilizador del ánimo es variable. Alrededor de la mitad de los pacientes presenta una respuesta incompleta. Parece que un 20-30% son buenos respondedores y que el grupo respondedor del no respondedor muestra diferencias fenotípicas y genéticas (76). Los estudios de familia muestran un patrón de respuesta hereditario entre generaciones (77). Se han estudiado diversos genes candidatos asociados a la respuesta al litio como son genes que codifican para el GSK3b, BDNF o el transportador de la serotonina (78). Los resultados de estas variantes muestran un efecto ligero sugiriendo una naturaleza poligénica de la respuesta del litio. Recientemente se han llevado a cabo diversos estudios de asociación del genoma completo (GWAS) y estudios transcriptómicos encontrando que la adhesión focal, la matriz extracelular y los *networks* de señalización de P13K-Akt se asociaban a buena respuesta del litio, datos que han sido parcialmente reproducidos (79), apuntando que los respondedores al litio son el resultado de un mecanismo diferente al de los no respondedores.

En los últimos años diversos estudios han mostrado que el litio modifica la expresión de los miARNs (secuencias de ARN, no codificantes, capaces de regular la expresión génica, que juegan un papel en los procesos celulares incluyendo desarrollo,

función y supervivencia) sugiriendo que éstos podrían tener un papel en la modulación de la eficacia clínica del litio, abriendo una nueva vía de estudio de los mecanismos de respuesta clínica del litio (80, 81).

5.3.2 Características farmacocinéticas del litio

El litio se absorbe fácilmente en el tracto gastrointestinal superior después de la ingesta oral. Las concentraciones plasmáticas máximas de litio se alcanzan entre 0,25 y 3 horas después de la ingesta oral de formulaciones de liberación inmediata y entre 2 y 6 horas con formulaciones de liberación lenta y controlada. La distribución del litio en el cuerpo se parece mucho a la del agua corporal total. Al alcanzar el equilibrio, el volumen aparente de distribución de litio puede oscilar entre 0,7 y 1 L/kg. No sufre ninguna transformación metabólica y su unión a las proteínas plasmáticas es mínima. Se excreta principalmente a través de la orina, aunque también se pierden pequeñas cantidades por el sudor y las heces. Se filtra a través de los glomérulos renales como ion libre y el túbulo proximal renal reabsorbe entre el 70 y el 80%. La eliminación del litio suele ser del 20 al 30% de la tasa de filtración glomerular (TFG) y, por tanto, varía con ella. La vida media de eliminación del litio oscila entre 18 y 36 horas en las personas menores de 40 años. Las concentraciones en estado estacionario se alcanzan en 4-5 días (82).

5.3.3 Indicaciones de uso del litio

La FDA aprobó el tratamiento con litio para los episodios maníacos del trastorno bipolar en 1970 y como tratamiento de mantenimiento para pacientes bipolares con antecedentes de manía en 1978 (83). También existe evidencia de su eficacia como potenciador en el tratamiento de la depresión refractaria, así como en el tratamiento de los síntomas afectivos en el trastorno esquizoafectivo (84, 85). El litio se asocia con una reducción del riesgo de suicidio en pacientes con trastorno bipolar (86). Ha demostrado ser eficaz como tratamiento de mantenimiento del trastorno bipolar perinatal y para prevenir la psicosis posparto (87, 47). El litio generalmente requiere aproximadamente

entre 1 a 3 semanas para iniciar su efecto, motivo por el que en la práctica el tratamiento de una manía aguda se opta por utilizar el litio en combinación con antipsicóticos (88). En la actualidad, las guias internacionales consideran el litio como el tratamiento de mantenimiento a largo plazo de TB (89).

El litio se considera un tratamiento de primera línea en el período perinatal en la mayoría de las guías internacionales (89) en parte debido a que ofrece la mejor relación de seguridad/eficacia tanto para la madre como para el feto/neonato en comparación con otros estabilizadores de ánimo, el ácido valproico y la carbamazepina que son fármacos teratogénicos conocidos (21, 90); en parte, porque otros fármacos como la lamotrigina o los antipsicóticos pueden ser menos eficaces (91, 21). Especialmente para las mujeres afecta de trastorno bipolar y estabilizadas con litio preconcepcionalmente, el uso mantenido de litio durante el embarazo y el posparto puede representar la mejor opción riesgo-beneficio (92).

La dosis de inicio recomendada es de 12-24 mmol (450-900 mg) de carbonato de litio al día y la dosis diaria de mantenimiento habitual es de 25 a 35 mmol (925 a 1300 mg) de carbonato de litio para pacientes menores de 40 años (82). El rango de concentración sérica óptima más común es de 0,5 a 0,8 mEq/L, con la opción de reducirlo a 0,40-0,60 mEq/L en caso de buena respuesta, pero mala tolerancia o de aumentarlo a 0,80-1,00 mEq/L en caso de respuesta insuficiente y buena tolerancia (93). El litio presenta una alta variabilidad intra e interindividual en la relación dosis-concentración, y factores como el embarazo, el cumplimiento inconsistente, la depleción de sodio, la deshidratación, la dieta, las interacciones medicamentosas, la enfermedad renal y las complicaciones obstétricas y del parto (ej.: hiperemesis gravídica, náuseas y vómitos, síntomas de trabajo de parto prematuro o preeclampsia, hemorragia posparto) pueden influir en los niveles séricos de litio (94).

5.3.4 Formas de dosificación disponibles y monitorización terapeútica

Las sales de litio están disponibles como citrato de litio, carbonato de litio y sulfato de litio. El litio normalmente se administra por vía oral, ya sea en forma de comprimidos, cápsulas o solución líquida. Es importante especificar qué tipo de formulación se ha dispensado ya que tienen una biodisponibilidad diferente. En nuestro medio, la formulación disponible es la de comprimidos de liberación sostenida de 400 mg de carbonato de litio.

De acuerdo con el consenso del Grupo de Trabajo de la Sociedad Internacional de Trastornos Bipolares (93) se recomienda medir las concentraciones séricas en estado estacionario (logrado después de tomar litio de manera constante durante un mínimo de 5 días) a las 12 horas ± 2 horas después de la dosificación de litio. Los pacientes en dosis única diaria nocturna, a los que se monitoriza 12 horas posdosis, presentan unas concentraciones séricas de litio un 10-15% más elevadas que si se hubieran monitorizado a las 24 horas posdosis (94, 95).

5.3.5 Efectos adversos

El litio puede provocar diversos efectos adversos, a menudo relacionados con la concentración sérica de litio, siendo infrecuentes por debajo de 1,00 mEq/L. Los efectos gastrointestinales (nauseas vómitos y diarreas leves), el vértigo, la debilidad muscular y las somnolencias son frecuentes al inicio del tratamiento, pero desaparecen tras la estabilización de la dosis de litio. El temblor fino, la poliuria y la polidipsia leve (sensación de sed) pueden persistir. Algunas enfermedades dermatológicas como el acné, la psoriasis, el *rash* cutáneo y las úlceras cutáneas pueden agravarse con el tratamiento con litio. Los efectos metabólicos asociados al tratamiento con litio son el hipotiroidismo, la ganancia ponderal, la diabetes insípida nefrogénica y el hipoparatiroidismo (89).

5.3.6 Interacciones farmacológicas

Los fármacos que alteran las concentraciones séricas de litio deben de prescribirse de forma cuidadosa, se deben de monitorizar estrechamente las concentraciones séricas de litio y realizar los ajustes de dosis que sean necesarios (94).

La administración concomitante de fármacos diuréticos, en particular tiazidas, de fármacos antiinflamatorios no esteroides, de fármacos antagonistas del sistema renina-angiotensina o de metronidazol, pueden elevar las concentraciones séricas de litio. La coadministración de antidepresivos (ej.: antidepresivos tricíclicos, inhibidores selectivos de recaptación de serotonina, venlafaxina) con litio pueden incrementar los efectos serotoninérgicos, así como los efectos neurotóxicos del litio sin incremento de las concentraciones séricas de litio. Los pacientes en tratamiento concomitante con antipsicóticos y litio pueden presentar efectos secundarios neurológicos que van desde síntomas extrapiramidales hasta el síndrome neuroléptico maligno (ej.: haloperidol + litio) (96).

5.3.7 Contraindicaciones del tratamiento con litio

Solo existen tres contraindicaciones absolutas para el tratamiento con litio: el fracaso renal agudo, el infarto agudo de miocardio y la hipersensibilidad al litio (89).

Si la indicación de mantener el tratamiento con litio se debe a un trastorno psiquiátrico grave que no ha respondido a otros estabilizadores del ánimo, las siguientes condiciones médicas suponen solo una contraindicación relativa al tratamiento con litio:

1. Insuficiencia renal: en pacientes con insuficiencia renal grave con un aclaramiento de creatinina inferior a 30 ml/min y que requieren una dieta baja en sodio se debe valorar la retirada del tratamiento con litio

2. Enfermedad cardiovascular: el litio induce alteraciones reversibles de la onda T y puede desenmascarar una arritmia cardiaca (síndrome de Brugada) por lo que se desaconseja su uso.

3. Hiponatremia: el litio disminuye la reabsorción de sodio en los túbulos renales, lo que provoca una depleción de sodio. La corrección rápida de niveles séricos de sodio inferiores a 120 mEq/L aumenta el riesgo de presentar un síndrome de desmielinización osmótica. Si surgen síntomas neurológicos durante el tratamiento de la hiponatremia, se recomienda suspender la corrección de sodio para evitar daños permanentes.

4. Hipotiroidismo e hipertiroidismo: el litio se acumula en la glándula tiroides, inhibiendo la síntesis y liberación de la tiroides, lo que puede provocar hipotiroidismo. También se han documentado casos de hipertiroidismo, incluida la enfermedad de Graves, el bocio multinodular tóxico y la tiroiditis. Se debe de realizar un seguimiento estrecho de la función tiroidea durante todo el tratamiento con litio.

5. Hipercalcemia e hiperparatiroidismo: el uso prolongado de litio se asocia con hiperparatiroidismo e hipercalcemia persistentes. En casos de hipercalcemia grave, puede ser necesario suspender el litio. Se recomienda controlar periódicamente los niveles de calcio sérico y si son inferiores a 2,75 mmol/L se debe de adoptar una actitud conservadora.

5.3.8 Toxicidad del litio

Debido a su estrecho índice terapéutico (0,6-1,2 mEq/L), las concentraciones séricas de litio superiores a 2 mEq/L se consideran tóxicos. La toxicidad del litio puede provocar nefritis intersticial, arritmia, síndrome del seno enfermo, hipotensión, anomalías de la onda T y bradicardia. En casos raros, la toxicidad puede provocar un pseudotumor cerebral. No existe ningún antídoto para la toxicidad del litio. El tratamiento consiste en la interrupción del tratamiento con litio y la hidratación mediante solución salina normal

que facilite la excreción de litio. Cuando la litemia sea superior a 4 mEq/L o independientemente de la concentración sérica de litio en pacientes que presenten alteraciones del nivel de conciencia, mioclonias, convulsiones, arritmias potencialmente graves o colapso cardiopulmonar, se iniciará tratamiento con hemodiálisis (89).

5.3.9 Uso del litio en la etapa perinatal

Las mujeres que interrumpen el tratamiento con litio durante el período perinatal tienen un alto riesgo de recaída (56). La profilaxis continua con litio durante el embarazo puede no solo mantener la estabilidad del estado de ánimo de la mujer durante el embarazo sino también prevenir la recaída posparto (97) pero existen preocupaciones legítimas sobre su uso durante el embarazo y la lactancia. Ver **Tabla 4.1.**

Los informes del Registro Internacional de Bebés con Litio de la década de los años 1970 estimaron que el uso de litio durante el primer trimestre de gestación se asociaba con un mayor riesgo de malformaciones cardiacas y que la anomalía de Ebstein era aproximadamente 400 veces más común entre los fetos expuestos prenatalmente al litio que entre los no expuestos. Estos cálculos se basaron en un registro de casos descritos voluntariamente y que probablemente sobreestimaron el riesgo (98). Más recientemente, un estudio de cohorte retrospectivo de 1.325.563 mujeres embarazas expuestas y no expuestas a litio durante el primer trimestre de gestación, ha estimado que la magnitud de este efecto es menor de lo que se había postulado previamente y es dosis dependiente (99). El riesgo parece ser mayor para los defectos de obstrucción del tracto de salida del ventrículo derecho (muy probablemente la anomalía de Ebstein) que para otros defectos cardíacos. En este estudio, el riesgo de defectos de obstrucción del tracto de salida del ventrículo derecho fue de 0,60 por 100 nacidos vivos entre los lactantes expuestos al litio y de 0,18 por 100 entre los lactantes no expuestos. Observaron que el riesgo aumentaba a medida que aumentaba la dosis de litio. Para una dosis diaria de 600 mg o menos, el riesgo relativo fue de 1,11 (IC95%: 0,46, 2,64) y aumentó a 1,60 (IC95%: 0,67, 3,80) para una dosis de 601 a 900 mg. La asociación fue estadísticamente significativa sólo en

mujeres que recibieron una dosis de litio superior a 900 mg, con un riesgo relativo de 3,22 para cualquier malformación (IC95%: 1,47, 7,02) para más de 900 mg (99).

Los cambios renales asociados con el embarazo son responsables de alteraciones en la farmacocinética del litio que a su vez pueden afectar la eficacia y toxicidad del litio en la madre (12). En comparación con los niveles previos al embarazo, la tasa de filtración glomerular (TFG) aumenta alrededor del 40-50% y el aclaramiento de litio aumenta entre un 30% y un 50%, lo que puede requerir un ajuste de la dosis de hasta un 50% (100). Por otra parte, se sabe que el litio presenta un paso placentario completo y se equilibra entre la circulación materna y fetal en un amplio rango de concentraciones maternas (0,2 a 2,6 mEq/L) (101). Se ha sugerido que la acumulación de litio en el suero fetal puede estar asociada con una mayor tasa de complicaciones neonatales, a veces denominada "síndrome del bebé flácido" (102). Para minimizar el impacto neonatal, se ha recomendado a las mujeres suspender el tratamiento con litio ó reducir un 25-50% la dosis de litio 3-4 antes de la fecha prevista de parto. Mas recientemente, se ha observado una asociación entre concentraciones altas de litio en lactantes (>0,64 mEq/L), puntuaciones de Apgar de 1 minuto más bajas, estancias hospitalarias más prolongadas y tasas más altas de complicaciones neuromusculares y del sistema nervioso central (101). La exposición intrauterina al litio no aumenta el riesgo de secuelas neuroconductuales adversas en humanos (103).

También se ha visto que la supresión del tratamiento con litio 24-48 horas antes del parto supone una reducción de la litemia materna de media 0,28 mEq/L sin que haya supuesto ningún riesgo de descompensación materna (101). En el posparto temprano, el volumen vascular disminuye rápidamente en aproximadamente un 40%, la hiperfiltración continúa a niveles un 20% por encima de lo normal en la semana 2 posparto y regresa a los niveles previos al embarazo entre 2 y 10 semanas después del parto (104). En aquellas mujeres que hayan precisado incremento de la dosis de litio en el tercer trimestre incrementa el riesgo de intoxicación materna (3).

Debido al peso molecular muy bajo (7D) y a la falta de unión a proteínas, el litio se transfiere fácilmente a la leche materna (18). El litio excretado en la leche materna humana es muy variable y representa aproximadamente el 50% (rango 0,17-1,07 %) de la concentración sérica de la madre (105). Ello ha llevado a que algunas directrices internacionales y expertos hayan postulado la exposición de los lactantes al litio supera los beneficios de la lactancia materna (106).

5.4 USO DEL LITIO EN EL EMBARAZO: EVALUACIÓN RIESGO-BENEFICIO

La Organización Mundial de la Salud (OMS, 2013) (107) define la atención preconcepcional como “la provisión de intervenciones de salud biomédica, conductual y social” a las mujeres y a sus parejas antes de la concepción, destinadas a mejorar su estado de salud y reducir comportamientos y factores de riesgo individuales y ambientales que podrían contribuir a una mala salud materna e infantil". El Instituto Nacional de Salud y Excelencia Clínica del Reino Unido (The National Institute for Health and Care, por sus siglas en inglés NICE) recomienda que a las mujeres en edad fértil que presenten un problema de salud mental moderado-grave *de novo*, existente o pasado se les ofrezca una consulta de asesoramiento psiquiátrico preconcepcional (108). Debido a que el estado de salud mental y los factores de riesgo pueden variar en el tiempo, este asesoramiento deberá realizarse varias veces durante la vida reproductiva de la mujer, aumentando así sus oportunidades de educación y maximizando potencialmente sus resultados reproductivos y de embarazo (109). Ver **Figura 5.**

La enfermedad materna no tratada tiene un impacto sobre la salud materna (ej.: malnutrición e incumplimiento de pautas médicas, aumento del consumo de tabaco, alcohol y otras drogas), sobre los resultados obstétricos y neonatales (aumento del riesgo de parto prematuro, bajo peso al nacimiento, aumento del riesgo de abortos espontáneos, aumento del riesgo de preeclampsia, aumento del riesgo de parto distócico, pobre adaptación neonatal, alteraciones del sueño y dificultades en la alimentación en el neonato) y sobre el neurodesarrollo (dificultades en la regulación del afecto, efecto negativo en el vínculo materno-infantil).

El proceso de asesoramiento psiquiátrico preconcepcional consta de un mínimo de dos visitas que se realizarán en un periodo máximo de 3 meses, en función del tiempo necesario para la obtención de los datos clínicos, de las exploraciones complementarias y de los informes de otros especialistas (en caso de presentar comorbilidad médica) que permitan acordar un plan de tratamiento psiquiátrico preconcepcional individualizado. Se

recomienda realizar esta consulta en un período de estabilidad psicopatológica de la mujer y cuando manifieste deseo gestacional para el año siguiente (110, 111).

El asesoramiento psiquiátrico preconcepcional implica una recogida exhaustiva transversal y longitudinal de:

1. Los antecedentes psiquiátricos personales: edad de inicio de la enfermedad psiquiátrica, edad de inicio del seguimiento psiquiátrico y/o psicológico, edad de inicio del tratamiento psicofarmacológico y/o psicológico, número de episodios tratados y no tratados, número de ingresos hospitalarios psiquiátricos, tiempo máximo de duración del ingreso psiquiátrico, última descompensación psiquiátrica con o sin ingreso hospitalario, antecedentes de autolesiones, número de tentativas autolíticas y tipo, así como fecha y tipo de la última tentativa autolítica, antecedentes de psicopatología en la etapa perinatal.

2. Los tratamientos psicofarmacológicos realizados: tipo de psicofármaco, dosis, frecuencia, efectos adversos relacionados, respuesta y motivo de retirada; máximo tiempo de estabilidad clínica con y sin tratamiento psicofarmacológico; tiempo máximo de estabilidad clínica tras la retirada del tratamiento psicofarmacológico; tiempo necesario para la estabilidad clínica tras el reinicio del tratamiento psicofarmacológico

3. Los tratamientos psicoterápicos realizados: tipo de tratamiento actual y pasado, así como respuesta al mismo y efectos secundarios.

Se evaluarán de forma detallada los antecedentes toxicológicos, médico-quirúrgicos, gineco-obstétricos y psiquiátricos de la paciente, así como los antecedentes médicos y psiquiátricos de los familiares de hasta tercer grado de consanguinidad. Se realizará un árbol genealógico, prestando especial atención a la presencia de enfermedades genéticas en la familia y su patrón de heredabilidad, así como a los trastornos psiquiátricos específicos de la etapa perinatal y su presentación en familiares

mujeres (madre y hermanas) de la paciente. Continuará con la realización de una evaluación psicopatológica completa (evaluación de áreas funcionales) y la solicitud de exploraciones complementarias según la patología psiquiátrica y tipo de tratamiento psicofarmacológico (p.ej., litemia) que esté realizando

Finalmente, se iniciará el proceso decisional compartido: el profesional de la salud informará a la paciente de los riesgos y beneficios de las diferentes alternativas terapéuticas existentes para el manejo de su trastorno psiquiátrico en base a la mejor evidencia científica existente en el momento de la evaluación. Se evaluarán las expectativas, valores y preferencias de la paciente respecto al tratamiento a seguir (psicofarmacológico y/o psicoterápica) durante el período perinatal (preconcepción, embarazo, parto, lactancia y primer año posparto). La guía de decisiones personales de Ottawa es un instrumento que permite a la paciente que pueda identificar sus necesidades de toma de decisiones, planificar los siguientes pasos, realizar un seguimiento de su progreso y compartir sus puntos de vista sobre la decisión (112). La escala de conflicto decisional ayudará a la monitorización del proceso decisional. Se realizarán las recomendaciones sobre los cambios de hábitos para una vida saludable en la etapa perinatal (dieta equilibrada, ejercicio, medidas higiénicas del sueño, cesación del consumo de tabaco, alcohol, cafeína y/o otras drogas de abuso).

Si la paciente presenta dificultades (conflicto decisional) que le lleve a postponer su decisión se podrán programar visitas sucesivas orientadas a ayudar en el proceso decisional y se incluirá una valoración del plan de tratamiento anticonceptivo (revisión de las interacciones de los anticonceptivos con el tratamiento farmacológico actual, así como el impacto de la elección de anticonceptivos en el estado de ánimo (61, 113).

Figura 5. Balance decisional riesgo-beneficio de realizar tratamiento con litio en el embarazo.

Figura creada por la autora.

Una razón común para no iniciar o suspender la lactancia materna es el uso de fármacos por parte de la madre lactante. Cualquier decisión terapéutica farmacológica durante la lactancia debe guiarse por la mejor evidencia disponible y la importancia del beneficio para cada paciente. Los factores que influyen en la decisión de amamantar convergen en torno a las ventajas y riesgos de la lactancia materna para la madre y el bebé, las características sociodemográficas y clínicas de la madre, la experiencia personal y la tradición familiar, la presencia de un sistema de apoyo (ya sea profesional o de pareja, familiar, social) y la elección personal. El momento óptimo para explorar las preferencias de las mujeres en cuanto a la lactancia materna y educar a la familia sobre las opciones de tratamiento durante la lactancia es antes de la concepción o al principio del embarazo. Las opciones incluyen realizar lactancia materna exclusiva, lactancia materna

complementada con fórmula o alimentación exclusiva con fórmula. Si la madre ha realizado un tratamiento farmacológico durante la gestación que ha llegado al feto en dosis plenas, no existe razón alguna para desaconsejar la lactancia materna. La exposición del lactante al fármaco a través de la lactancia materna es inferior a la exposición fetal (114). Ver **Figura 6.**

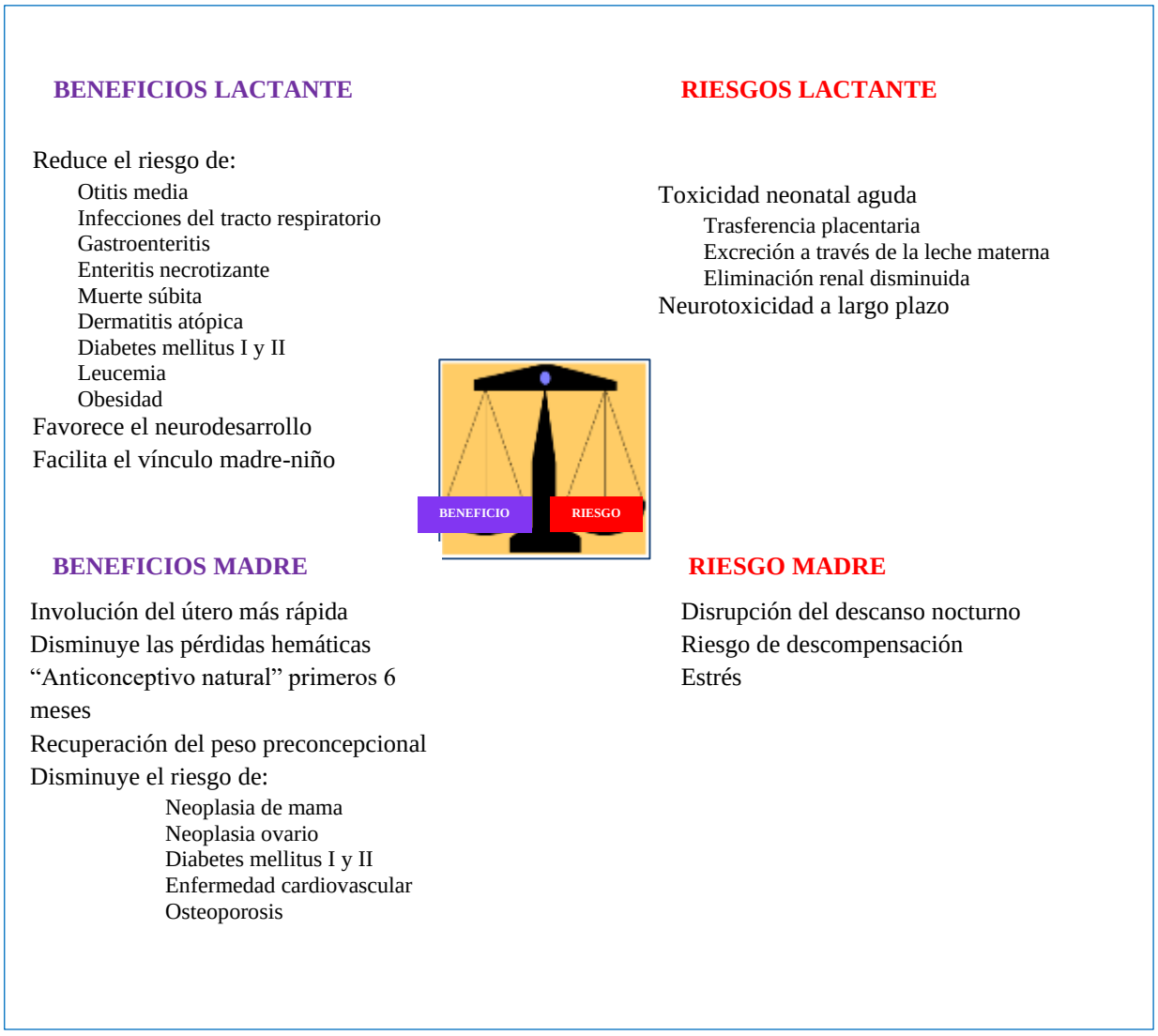


Figura 6. Balance decisional riesgo-beneficio de realizar lactancia materna en mujeres lactactes en tratamiento farmacológico.

Figura creada por la autora.

Organizaciones profesionales como la Academia Estadounidense de Pediatría (AAP, 2012) (115), la Organización Mundial de la Salud (OMS, 2017) (116) recomiendan la lactancia materna exclusiva durante los primeros 6 meses de vida siempre que sea posible, seguido de una combinación de leche materna con alimentos complementarios adecuados hasta que el bebé tenga entre 1 y 2 años o más (117).

Las ventajas en recién nacidos y lactantes incluyen un riesgo reducido de infecciones como otitis media e infecciones del tracto respiratorio, síndrome de muerte súbita del lactante, dermatitis atópica, enfermedad inflamatoria intestinal, diabetes mellitus tipo 1 y 2, leucemia y obesidad (118, 119). La lactancia materna también se asocia con un mejor desarrollo neurológico (120) y el vínculo entre madre e hijo (121).

Además, la madre lactante obtiene beneficios de la lactancia materna, como una involución uterina más rápida, una menor pérdida de sangre posparto, una reducción de la fertilidad y un retorno más temprano al peso que tenía antes del embarazo, y también un riesgo reducido de cáncer de mama y de ovario, y diabetes tipo 1 y 2. mellitus y enfermedades cardiovasculares y posiblemente también fractura de cadera y osteoporosis en el período posmenopáusico (118, 119).

Existen pocas contraindicaciones para la lactancia materna como son la infección materna por el VIH y por el virus linfotrópico de células T humanas tipo 1 o 2, la tuberculosis activa no tratada o lesiones de herpes simple en la mama. Además, el uso materno de drogas ilícitas (es decir, fenciclidina o cocaína), agentes quimioterapéuticos (drogas que interfieren con la replicación celular) y terapias con isótopos radiactivos deberían contraindicar la lactancia materna.

El uso del litio uso durante la lactancia resulta controvertido (122). Debido a la alta variabilidad de su difusión en la leche materna, se ha sugerido que puede producirse una toxicidad neonatal/lactante por litio, así como que puede asociarse con un riesgo de recaída materna secundaria a la fragmentación del sueño (89, 118). Nos propusimos revisar sistemáticamente la evidencia y la calidad de los estudios clínicos de lactancia materna con litio aquel nos ayudara a tomar decisiones fundamentadas.

5.5 REVISIÓN SISTEMÁTICA: "Estudios clínicos de lactancia materna con litio"

Imaz ML, Torra M, Soy D, García-Esteve L, Martin-Santos R. Clinical Lactation Studies of Lithium: A Systematic Review.Front Pharmacol. 2019; 10: e1005.

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Introducción: El objetivo del presente artículo fue revisar sistemáticamente la evidencia actual y la calidad de los estudios que evalúan la transferencia de litio a los lactantes y sus resultados a corto plazo. Existe evidencia sustancial de que la profilaxis posparto con litio reduce la tasa de recaída en el trastorno bipolar. Sin embargo, está contraindicado durante la lactancia debido a la alta variabilidad de la transferencia a la leche materna.

Objetivos: Realizamos una revisión sistemática de la evidencia actual de los estudios que evalúan la transferencia de litio a los lactantes y los resultados infantiles a corto plazo.

Método: Se diseñó un protocolo a priori basado en las directrices PRISMA. Se realizaron búsquedas en PubMed y LactMed hasta septiembre de 2018. Se incluyeron estudios que evaluaron los parámetros farmacocinéticos del litio y los resultados infantiles a corto plazo. La calidad se evaluó mediante una lista de verificación basada en directrices internacionales (es decir, FDA).

Resultados: De 344 estudios iniciales, se incluyeron 13 informes de casos/series con 39 díadas madre-hijo. Sólo el 15% de los estudios cumplieron con ≥50% de los ítems de la lista de verificación de evaluación de calidad. Los lactantes amamantan una media (DE) de 58,9 (83,3) días. La dosis materna media de litio fue de 904 (293) mg/día, la concentración correspondiente de litio en plasma/suero fue de 0,73 (0,26) mEq/L y la concentración en la leche materna fue de 0,84 (0,14) mEq/L. La concentración media de litio en plasma/suero del lactante fue de 0,23(0,26) mEq/L. Veintiséis (80%) lactantes tuvieron concentraciones ≤0,30 mEq/L sin efectos adversos. Ocho (20%) mostraron un evento adverso transitorio (es decir, toxicidad aguda o alteraciones de la tiroides). Todas ellas también estuvieron expuestas prenatalmente a monoterapia o politerapia con litio.

Conclusiones: La evidencia actual proviene de estudios con cierto grado de heterogeneidad y de calidad baja-moderada. Sin embargo, identifica áreas de mejora para futuros estudios clínicos de lactancia con litio y respalda algunas recomendaciones clínicas.

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SYSTEMATIC REVIEW
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Clinical Lactation Studies of Lithium: A Systematic Review

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Background: There is substantial evidence that postpartum prophylaxis with lithium lowers the rate of relapse in bipolar disorder. However, it is contraindicated during breastfeeding due to the high variability of the transfer into breast milk.

Aims: We conducted a systematic review of the current evidence of studies assessing the transfer of lithium to lactating infants and short-term infant outcomes.

Methods: An *a priori* protocol was designed based on PRISMA guidelines. Searches in PubMed and LactMed were conducted until September 2018. Studies assessing lithium pharmacokinetic parameters and short-term infant outcomes were included. Quality was assessed using a checklist based on international guidelines (i.e., FDA).

Results: From 344 initial studies, 13 case reports/series with 39 mother–child dyads were included. Only 15% of studies complied with ≥50% of the items on the quality assessment checklist. Infants breastfeed a mean (SD) of 58.9 (83.3) days. Mean maternal lithium dose was 904 (293) mg/day, corresponding lithium plasma/serum concentration was 0.73(0.26) mEq/L, and breast milk concentration was 0.84(0.14) mEq/L. Mean infant lithium plasma/serum concentration was 0.23(0.26) mEq/L. Twenty-six (80%) infants had concentrations ≤0.30 mEq/L without adverse effects. Eight (20%) showed a transient adverse event (i.e., acute toxicity or thyroid alterations). All of them were also prenatally exposed to lithium monotherapy or polytherapy.

Conclusion: The current evidence comes from studies with a degree of heterogeneity and of low-moderate quality. However, it identifies areas of improvement for future clinical lactation studies of lithium and provides support for some clinical recommendations.

Keywords: lithium, lactation, breastfeeding, human milk, postpartum, neonates, nursing infants, systematic review

INTRODUCTION

Over the past decades, evidence of the health advantages of breastfeeding for neonates/infant and mothers has continued to increase, and many recommendations for practice have been published. Currently, professional organizations including The American Academy of Pediatrics (AAP, 2012), The American College of Obstetricians and Gynecologists (ACOG, 2013), and the World Health Organization (WHO, 2017) recommend breastfeeding exclusively for the first 6 months of life whenever possible, followed by combining breast milk with adequate complementary foods until the infant is 1–2 years old or beyond (Victora et al., 2016). Advantages in newborn and infants include a reduced risk of infections such as otitis media and respiratory tract infections, sudden infant death syndrome, atopic dermatitis, inflammatory bowel disease, type 1 and 2 diabetes mellitus, leukemia, and obesity (AAP, 2012; Bartick et al., 2017). Further, breastfeeding is also associated with improved neurological development (Kramer et al., 2008) and mother–infant bonding (Britton et al., 2006). In addition, the nursing mother derives benefits from breastfeeding, such as more rapid uterine involution, decreased postpartum blood loss, fertility reduction and earlier return to pre-pregnancy weight, and also a reduced risk of breast and ovarian cancers, type 1 and 2 diabetes mellitus, and cardiovascular disease and possibly also hip fracture and osteoporosis in the postmenopausal period (AAP, 2012; Bartick et al., 2017).

Bipolar disorder is considered a severe mental disorder that usually starts in the late teens and early twenties and is characterized by episodes of mania, depression, hypomania, and mixed episodes (Leboyer et al., 2005). Studies have shown that female patients with bipolar disorder are at a high risk of symptom relapse during pregnancy (Viguera et al., 2011) and the early postpartum period (Munk-Olsen et al., 2009; Viguera et al., 2011). With regard to the postpartum risk, studies have shown that 40–70% of untreated bipolar women may experience postpartum episodes of the condition (Viguera et al., 2000). There is substantial evidence that postpartum prophylaxis with mood stabilizers lowers the rate of relapse (Steward et al., 1991; Cohen et al., 1995; Bergink et al., 2012).

Lithium remains a first-line treatment for bipolar disorder during the perinatal period, given its favorable safety profile compared to other mood stabilizers (valproate, carbamazepine) (Gentile, 2012; Khan et al., 2016). The Food and Drug Administration approved lithium treatment for manic episodes of bipolar disorder and for bipolar depression, and as maintenance treatment for bipolar patients with a history of mania (López-Muñoz et al., 2018). It is also prescribed as adjunctive treatment in major depressive disorder (Bauer et al., 2003). Lithium appears to reduce the risk of suicide in patients with bipolar disorder (Cipriani et al., 2013), and it has been shown to be effective in reducing the risk of postpartum relapse (Bergink et al., 2015).

Lithium (Li^{3+}) is the third element in the periodic table and is a monovalent cation that shares certain properties with sodium, potassium, and calcium. Its specific mechanisms of action in stabilizing mood are not yet well understood. At neuronal level, lithium reduces excitatory neurotransmission (i.e., of dopamine and glutamate) but increases inhibitory neurotransmission (i.e., of GABA). It may alter intracellular signaling through action on second messenger systems. Specifically, it inhibits inositol monophosphatase, possibly affecting neurotransmission *via* the phosphatidylinositol second messenger system, and it also reduces protein kinase C activity, possibly affecting the genomic expression associated with neurotransmission (Malhi et al., 2013).

Lithium is absorbed rapidly and completely after oral intake. Peak levels occur within 1 to 3 h with standard preparations and within 4 to 4.5 h with the slow and controlled release forms. It is not metabolized or bound to proteins. It is eliminated almost exclusively *via* the kidneys, although small amounts are also lost in sweat and feces, and 70–80% is reabsorbed primarily in the proximal tubule of the kidney. Lithium's elimination half-life is about 18–24 h in healthy young subjects. Steady state concentrations are achieved within 4–5 days (Alda, 2006; Malhi et al., 2013). The target plasma level for lithium in acute treatment is 0.8–1.2 mEq/L in young subjects, while in maintenance treatment, the most common optimal plasma concentration range is 0.5–0.8 mEq/L (Gelenberg et al., 1989; Malhi et al., 2017; Hiemke et al., 2018).

Physiological changes during pregnancy (Feghali et al., 2015) may alter the pharmacokinetics of lithium and can cause a notable decline in maternal lithium serum concentrations during this period. In the third trimester, lithium clearance rose by 30–50% (Grandjean and Aubry, 2009; Westin et al., 2017; Wesseloo et al., 2017) because of increased plasma volume and greater glomerular filtration rate (Davison and Dunlop, 1980; Deligiannidis et al., 2014). Lithium has a complete placental passage with ion equilibration across placental barrier that is remarkably uniform across a wide range of maternal concentrations (0.2–2.6 mEq/L) (Newport et al., 2005). Its levels rise slightly in the immediate postpartum (Wesseloo et al., 2017) because the glomerular filtrate returns to pre-pregnancy levels after delivery (Davison and Dunlop, 1980; Deligiannidis et al., 2014). Use of lithium in late pregnancy may produce toxicity in the newborn: this is usually transient and reversible, but neonates may present respiratory distress syndrome, cyanosis, lethargy, depressed neonatal reflexes, hypotonia, bradycardia, and feeding difficulties (Kozma, 2005; McKnight et al., 2012). These complications are associated with lithium concentrations in cord blood above 0.64 mEq/L (Newport et al., 2005). In this situation, neonates may require supportive care for 10–14 days until they eliminate lithium. No long-term neurodevelopmental effects have been reported in infants exposed to lithium in utero (Schou, 1976; Van der Lugt et al., 2012; Poels et al., 2018).

With regard to breastfeeding, lithium is excreted in human breast milk at a mean rate of approximately 50% (range 0.17–1.07%) of the mother serum concentration (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen and Hertz, 1972; Schou and Amdisen, 1973; Sykes et al., 1976; Viguera et al., 2007; Tanaka et al., 2008). First 4 to 10 days postpartum, lithium can pass between alveolar cells because large gaps exist. By the end 1st week postpartum, alveolar cells swell under influence of prolactin, closing the intracellular gaps, and limiting access to the milk (Pons et al., 1994) (**Figure 1**). Factors that affect the passage of a drug into breast milk include route of administration, absorption rate, half-life, peak serum

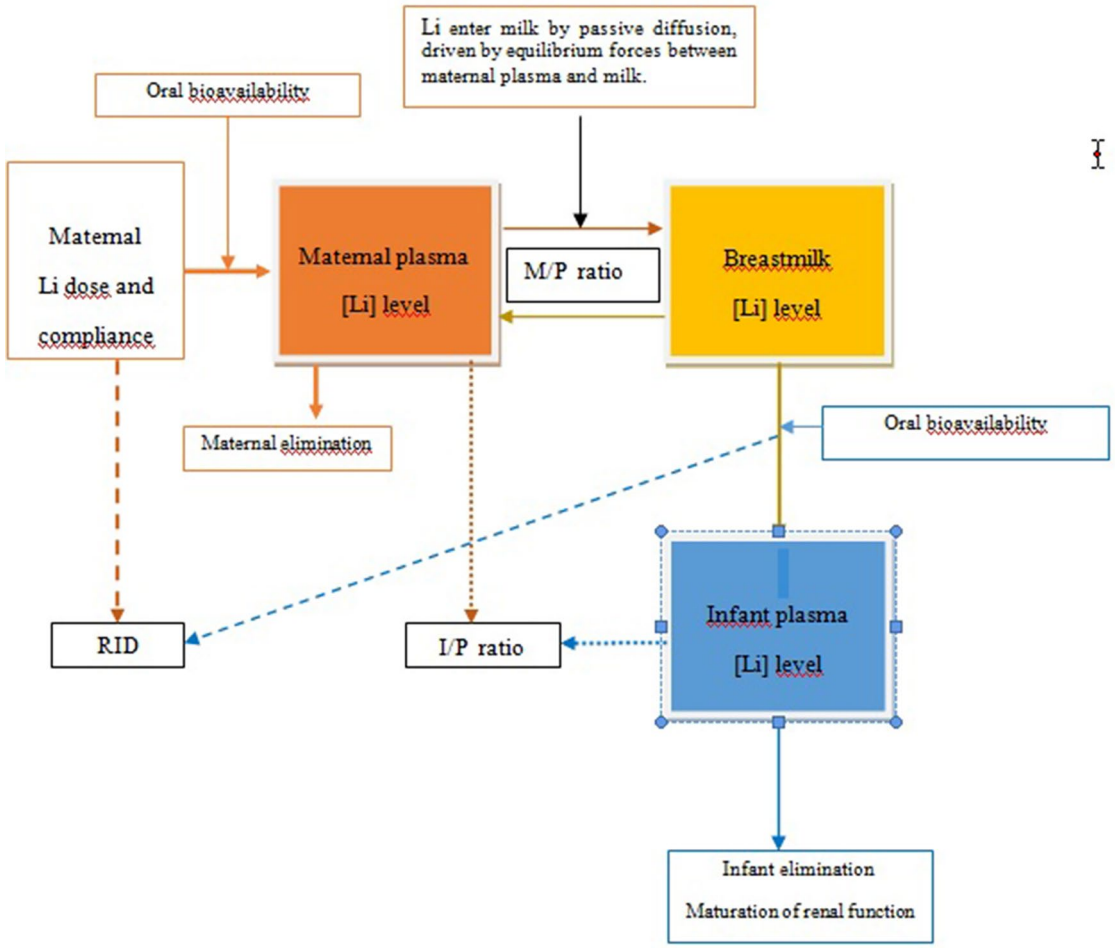

FIGURE 1 | Transfer of lithium from mother to infant *via* breastmilk. I, infant plasma; M, milk; P, maternal plasma; RID, relative infant dose.

time, dissociation constant, volume of distribution, molecular size, protein binding, degree of ionization, pH, and solubility (Lawrence, 1994; Tanaka et al., 2008). Because of its very low molecular weight and lack of protein binding, lithium is readily transferred into breast milk. The amount of drug received by the infant also depends on multiple factors: milk yield and composition (i.e., colostrum *versus* mature milk), concentration of the drug in the milk, which breast is being suckled (as the yield from each breast is not equal), and how well the breast was emptied during the previous feeding (Lawrence, 1994; Pons et al., 1994). However, the mean volume of milk transferred to the infants is lower during the first 2 days after delivery and increases rapidly on days 3 and 4, and then more slowly to a maximum of approximately 800ml/day at 6 months of age (Neville et al., 1988). An infant's ability to absorb, detoxify, and excrete the drug are important factors (Lawrence, 1994). Less mature infants are less able to clear drugs because of their immature liver and renal functions (Pons et al., 1994), and so medications that are predominately eliminated through the kidney, such as lithium, may accumulate (Flaherty and Krenzelok, 1997). The infant's age also affects the amount of milk consumed, since in older infants nourishment is supplemented (AAP, 2012; ACOG, 2013; Victora et al., 2016; WHO, 2017). Other factors include any medical problems that the infant may have. At present, no information on lithium exposure *via* breast milk for preterm or ill infants is available (Bogen et al., 2012).

Although lithium is contraindicated during breastfeeding in many treatment guidelines (Hirschfeld et al., 2002; National Institute for Health and Clinical Excellence (NICE), 2014; Malhi et al., 2015; McAllister et al., 2017; Yatham et al., 2018) due to the high variability of the transfer into breast milk, other sources do not argue against its use (Uguz and Sharma, 2016; Pacchiarotti et al., 2016) especially when maternal mood is stable, during lithium monotherapy (Viguera et al., 2007) and in healthy infants over 2 months of age (Anderson et al., 2003; Soussan et al., 2014; Anderson et al., 2016). Finally, other studies favor its use under strict infant clinical monitoring (Bogen et al., 2012).

In clinical practice, it is difficult to decide whether to initiate, maintain, or discontinue lithium treatment during breastfeeding. Increasingly, women with bipolar disorder are expressing a desire to breastfeed while receiving lithium (Galbally et al., 2018). Women who may benefit from lithium in the postpartum period and who want to breastfeed are encouraged to discuss

these decisions with their healthcare providers (obstetricians, psychiatrists, and pediatricians) in a collaborative manner.

The aim of the present paper was to systematically review the current evidence and quality of studies assessing the transfer of lithium to lactating infants, and their short-term outcomes.

METHODS

Data for this systematic review were collected with an advance protocol (see supporting information) based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). The protocol for this systematic review was published *via* PROSPERO (registration code CRD42019120928). Two of the authors (MLI, MT) independently reviewed all the studies retrieved, and differences in opinion were resolved by consensus, and when necessary after discussion with a third researcher (RMS) (see **Supplementary material**).

Search Strategy

Papers published in electronic databases including PubMed and LactMed between 1 January 1995 and 28 September 2018 were sought, using the following terms: "lithium," "lactation," "breastfeeding," "postpartum period," "puerperium," "neonates," and "nursing infants" mixed with Boolean operator "AND." Experimental studies involving animals, reviews or meta-analyses, letters to the editor, editorials, and commentaries were excluded. After the titles of all non-duplicated articles had been identified, the abstracts were screened to ensure that they met the inclusion criteria. Full texts of the relevant abstracts were obtained and examined carefully to determine their eligibility for inclusion. Additionally, references in the papers were examined in order to identify further relevant publications. We tried to get in contact with authors when missing data.

Study Selection

Only articles containing primary data in humans were considered for inclusion in the systematic review, in accordance with the following predefined criteria: (1) case reports, case series, case-control studies, cohort studies, quasi-experimental, or experimental studies; (2) studies that monitored lithium concentration in mother (plasma/serum and/or breast milk) and infants (plasma/serum) during the lactation period; (3) use of clearly defined pharmacokinetic parameters such as the infant-plasma concentration and/or the milk-to-plasma ratio (M/P ratio), relative infant dose (RID), and/or the infant-plasma-to-maternal plasma ratio (I/P ratio); (4) type of concomitant medication used; (5) well-defined adverse events or developmental outcomes in the infants; and (6) studies published in English or Spanish in a peer-reviewed journal.

Data Extraction and Main Outcomes

The variables recorded for each study were: author, year of publication, country, study design, sample size, maternal diagnosis, maternal weight, type of breastfeeding, duration of breastfeeding, medication regimen administered to the mother during pregnancy and lactation (lithium and concomitant drugs), type of delivery, gestational age, birth weight, infant sex, Apgar minutes 1–5, infant age at sampling (weeks + days), lithium plasma/serum concentrations in mother and infant, lithium milk concentrations, pharmacokinetic parameters, and neonate and infant adverse effects.

Assessment of Pharmacokinetic Parameters (Direct and Estimated)

The amount of drug transferred to infant was measured directly in infant-plasma/serum or estimated on the basis of pharmacokinetic parameters (M/P ratio or RID) (Begg et al., 2002; FDA, 2005; Sachs and Committee on Drugs, 2013).

Direct Measures

Infant-Plasma Drug Concentration (I)

The infant plasma/serum concentration provides information regarding the fraction of drug that is systematically available to the breastfed child (Begg et al., 2002). It is the most direct measure for risk assessment (FDA, 2005; European Medicine Agency, 2009). However, in women who take lithium in late pregnancy, infant levels measured in the early neonatal period (first 7–10 days postpartum) may reflect transplacental passage of lithium rather than its intake *via* breast milk (Hale and Rowe, 2017). Another point to take into account is that this invasive exploration may be painful for the infant and may be rejected by parents.

Toxic levels of lithium in plasma or serum have not been established. The best approximation at present is the case series study of 10 mother–infant pairs in which the mother received lithium monotherapy during pregnancy and lactation (Viguera et al., 2007). In this study, no infants showed signs and symptoms of lithium toxicity, and lithium infant-plasma levels were below 0.30 meq/L.

Estimated Measures

Milk-to-Maternal Plasma Drug Concentration Ratio (M/P Ratio)

The M/P ratio is an estimate of the distribution of the drug between maternal plasma and milk. It is calculated by dividing the concentration of the drug in the mother's milk by the concentration in the mother's plasma. The currently accepted method for calculating the M/P ratio is to use the ratio between the area under the curve (AUC) for milk and plasma. The calculation of the AUC from the collection of several samples (five or six) of steady state lithium over a specific time interval is probably the most suitable method (Begg et al., 2002) **Figure 1**.

A M/P ratio <1 is a good indicator that only minimal levels of the drug are transferred into the milk, while a ratio >1.5 implies that high levels of the drug may be sequestered in milk (Begg et al., 2002). From a clinical perspective, the M/P ratio does not predict the safety of a drug for the child during breastfeeding (Begg et al., 2002).

The Relative Infant Dose (RID)

The RID is calculated by dividing the infant's dose *via* milk in mg/kg/day by the maternal dose in mg/kg/day. This weight-normalizing method indicates approximately how much of the maternal dose the infant is receiving (**Figure 1**).

Several cutoff points have been proposed for this index (Atkinson et al., 1988). A RID <10% of the lowest end of the weight-adjusted maternal dosage is considered acceptable for breastfed infants, and RIDs >25% should be avoided in nursing mothers. Recently, a joint working group in Denmark developed guidelines for the use of psychotropic drugs during breastfeeding which used an equally arbitrary, but more conservative cutoff of 5% as the limit of breastfeeding acceptability (Larsen et al., 2015).

Although the RID is accepted as a measure of the safety of medication during breastfeeding, it has some limitations. For example, if the drug dose given to the mother increases, so does the infant's dosage received *via* breast milk, but the RID does not usually change. Therefore, the RID is unreliable for representing drug safety during breastfeeding for a drug with a wide dosage range, especially those with an RID near the 10% cutoff point. Another limitation is that the RID does not account for the possibility of differences in bioavailability of the drug related to infant age (Anderson and Sauberan, 2016).

The Infant-Plasma-to-Maternal Plasma Drug Concentration Ratio (I/P Ratio)

The I/P ratio is the concentration of drug in the infant's plasma divided by the concentration in the mother's plasma. The plasma concentration comparison is appealing because it minimizes variables such as bioavailability and differences in clearance between the infant and mother. It is most accurate when applied at steady-state for drugs that have a relatively long elimination half-life because maternal and infant levels do not fluctuate substantially. When samples are obtained in these conditions, a reliable measurement for single trough blood samples from the mother and infant would probably suffice, although this possibility has not been rigorously tested. For drugs with a short elimination of half-life, multiple plasma samples are required to obtain average plasma concentrations or AUC measurements to derive a reliable I/P ratio (Anderson and Sauberan, 2016). In the case of lithium, the half-life is about 18 to 24h in healthy young women, but it appears to be longer in neonates—close to 96 h with a high interindividual variability (range: 1.42–36.09 days) (Guitart et al., 2013).

As with the RID, a drug that produces a steady-state I/P ratio below 10% of the lowest end of the therapeutic concentration range was considered acceptable by the American Academy of Pediatric, and a ratio above 25% was considered unacceptable (Sachs and Committee on Drugs, 2013). A problem with the I/P ratio in relation to the time of infant sampling may occur if the mother was taking the drug during pregnancy. In general, a much larger amount of the drug is passed to the fetus transplacentally than to the infant *via* breast milk. Therefore, obtaining infant blood samples too soon after delivery (<7 days) may reflect transplacental passage rather than breast milk transfer (Hale and Rowe, 2017).

Quality Assessment

The quality review of all studies was based on the guidelines of the International Lactation Consultant Association, the Food and Drug Administration, and the European Medicine Agency (Begg et al., 2002; FDA, 2005; European Medicine Agency, 2009). These guidelines provide recommendations for conducting clinical lactation studies. We recorded data on study design, clinical conduct, endpoints correctly assessed, and laboratory methods in a checklist and also added one more item: the presence or absent of adverse events.

All studies that met the criteria were assessed using this checklist. Their quality was calculated by dividing the number of items scored by the total number of items and recorded as a percentage (**Table 3**).

RESULTS

Study Selection

Of 709 records, 366 were removed after screening due to duplication, and 302 were excluded after title/abstract review because they did not meet the selection criteria *a priori*. Forty two full texts were then assessed for eligibility. Of these, 29 articles were excluded for reasons shown in **Figure 2**. Articles were selected in accordance with the PRISMA statement, and the process is outlined in **Figure 2**.

Description of Studies

Thirteen studies—9 case reports (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen and Hertz, 1972; Sykes et al., 1976; Montgomery, 1997; Skausing and Shou, 1977; Tanaka et al., 2008; Marín et al., 2011; Frew, 2015) and 4 case series (Schou and Amdisen, 1973; Moretti et al., 2003; Viguera et al., 2007; Bogen et al., 2012) including a total of 40 mothers with severe mental disorders treated with lithium during lactation were published in the literature between 1969 and 2018. Twenty-nine mothers had bipolar disorder, 1 had recurrent depressive disorder, and in 10, the condition was not specified. Thirty-nine out of 40 mother–infant pairs had at least 1 simultaneous determination of lithium in the mother (serum or milk) and in the child (serum). All articles included were written in English or Spanish with the exception of one Danish article with an informative English abstract (Skausing and Shou, 1977). Thus, the final sample comprised 13 studies including 39 mother–infant cases.

Only one study each provided information on maternal ethnicity (Bogen et al., 2012) and weight (Moretti et al., 2003). Similarly, only one study provided information on smoking or alcohol status, or concomitant illness in pregnancy or postpartum (Moretti et al., 2003). Some studies reported the gravidity/parity index (Tunnessen and Hertz, 1972; Sykes et al., 1976; Bogen et al., 2012; Frew, 2015), gestational age (Tunnessen and Hertz, 1972; Sykes et al., 1976; Moretti et al., 2003; Tanaka et al., 2008; Bogen et al., 2012; Frew, 2015), and weight birth (Tunnessen and Hertz, 1972; Sykes et al., 1976; Tanaka et al., 2008; Marín et al., 2011; Bogen et al., 2012).

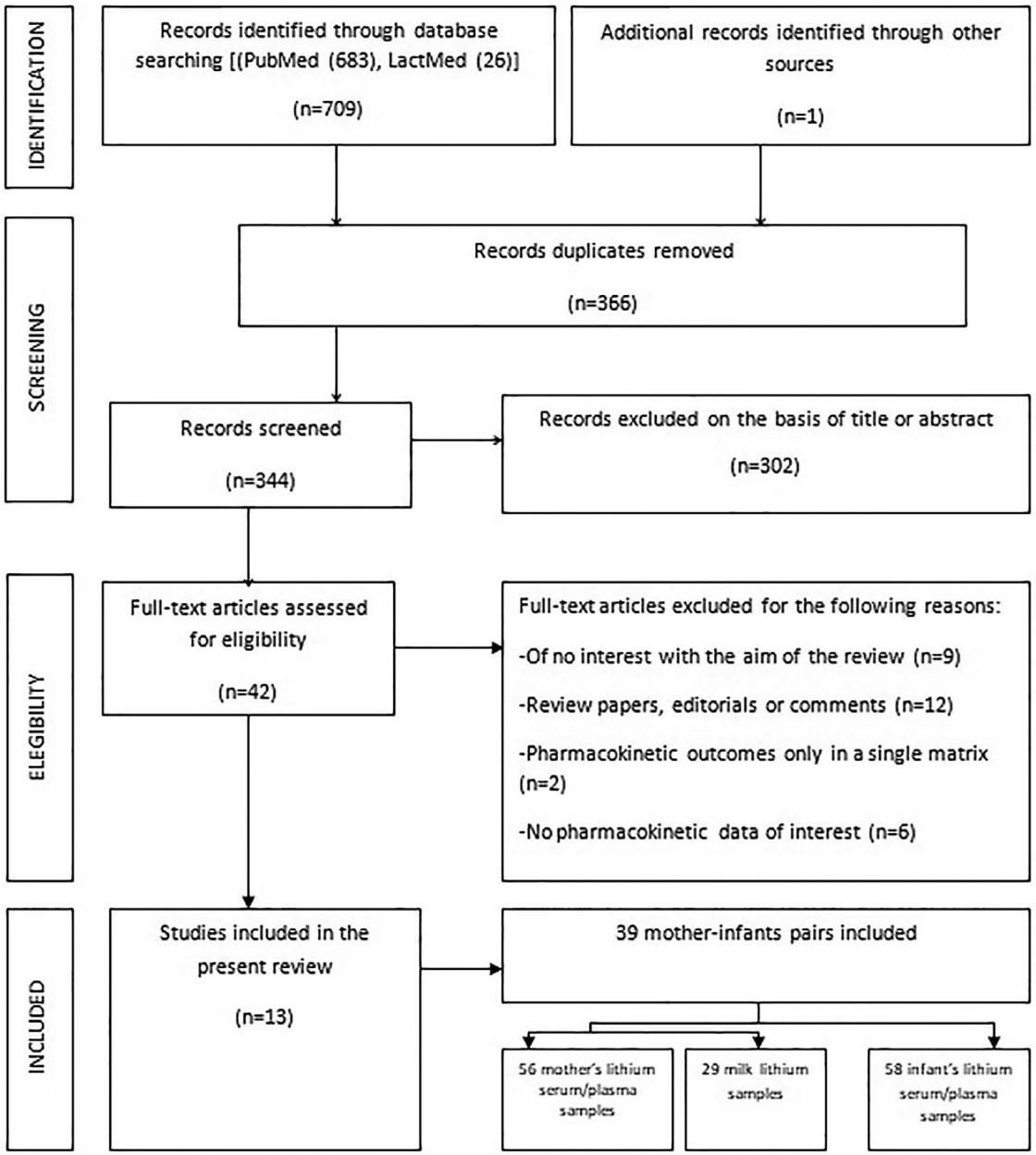

FIGURE 2 | Flowchart of considered and finally selected studies, according to the PRISMA statements.

From the 39 cases, 22 were treated with lithium during the index pregnancy (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen and Hertz, 1972; Sykes et al., 1976; Moretti et al., 2003; Viguera et al., 2007; Tanaka et al., 2008, Marín et al., 2011; Bogen et al., 2012; Frew, 2015), and in 17 cases, no information was provided. Moreover, four cases received polytherapy in pregnancy (Tunnessen and Hertz, 1972; Bogen et al., 2012), and 3 more during lactation (Sykes et al., 1976; Marín et al., 2011; Frew, 2015). Sixteen mothers practiced exclusive breastfeeding (Viguera et al., 2007; Marín et al., 2011; Bogen et al., 2012; Frew, 2015), and in the other cases, no information was available on the type of maternal lactation. **Table 1** summarizes the characteristics of the studies included.

Pharmacokinetic Results

The pharmacokinetic results (mean, SD, and range) are shown in **Table 2**. The 39 mother–infant pairs contributed 56 maternal serum samples, 29 maternal milk samples, and 58 infant serum samples. The samples were obtained in a very wide range between 1 day and 385 days postpartum. Infants were breastfed an average of 58.86 (83.25) days (SD), but in most studies, only one or a few measurements were recorded. The maternal daily dose of lithium was between 400 and 1,500 mg/day, with a mean (SD) of 904 (283) mg/day and corresponding mean (SD) lithium serum concentrations o 0.73 (0.26) mEq/L (0.12–1.50).

TABLE 1 | Characteristics of the studies included in the systematic review: maternal diagnosis, treatment during pregnancy and lactation, and obstetric and neonatal outcomes.

Author year/country	Study design, N	Mother–infant pair code$_n$	Pregnancy				Postpartum					
			Mother				Neonate				Mother	
			Age (years)	Diagnosis	Medication (mg/day)	[Li] (meq/L)	Type of delivery	Gestational age (weeks)	Birth weight (g), sex	Apgar 1/5 min	Medication (mg/day)	Type of breastfeeding
Weinstein and Goldfield, 1969/Sweden	Case report N = 1	1	NA	NA	Lithium 1,000	0.33–0.35	NA	NA	NA	NA	Lithium 1,000	Not specified
Fries, 1970/Sweden	Case report N = 1	2	NA	NA	Lithium 900	0.90	NA	NA	NA	NA	Lithium 900	Not specified
Tunnessen and Hertz, 1972/USA	Case report N = 1	3	31	RDD	Lithium 600–1,200[b] others[c]	1.07–1.38	Vaginal instrumented	38	2,910/F	6/9	Lithium	Not specified
Schou and Amdisen, 1973/Denmark	Case series N = 5	4–8	NA	NA	NA	NA	NA	NA	NA	NA	Lithium	Not specified
Sykes et al., 1976/UK	Case report N = 1	9	36	BD	Lithium 800–400	0.61–1.20 D: MP 0.32-UC 0.32	Vaginal instrumented	38	3,450/M	NA	Lithium: 400–800 others[e]	Not specified
Skausing and Schou, 1977/Denmark	Case report N = 1	10	NA	NA	NA	NA	NA	NA	NA	NA	Lithium	Not specified
Montgomery, 1997/USA	Case report N = 1	11	NA	NA	NA	NA	NA	NA	NA	NA	Lithium 900	Not specified
Moretti et al., 2003/Canada	Case series N = 11	12–22	NA	BD	Lithium	NA UC 0.43 (C_{18})	NA	NA 32 wk (C_{20})	NA	NA	Lithium 600–1,500 From month 15(C_{22})	Not specified Mixed 50/50 (C_{20})
Viguera et al., 2007/USA	Case series N = 10	23–32	NA	BD	Lithium 34wk-D (C_{28})	NA	NA	NA	NA 1 M/9 NA	NA	Lithium 600–1,200	Exclusive
Tanaka et al., 2008/Canada	Case report N = 2	33	32	BD	Lithium 1,500	0.34–0.48	NA	31	1,700/M	7/8	Lithium 1,200	Not specified initiated day 7
		34[a]	37	NA	Lithium 900	0.9 at delivery	NA	Full term	3,100/F	7/8	NA	Not specified
Marín et al., 2011/Spain	Case report N = 1	35	NA	BD	Lithium 800	NA	Caesarean section	40	3,140/M	9/10	Lithium 800 + others[e]	Exclusive
Bogen et al., 2012/USA	Case series N = 4	36	28	BD type I	Lithium 900 + others[c]	0.20–0.55 0.48 (–30 days)[d]	NA	40	3,405/M	8/9	Lithium 900	Exclusive
		37	30	BD type I	Lithium 900 + others[c]	0.60 (–14 days)[d]	NA	41	4,026/F	9/9	Lithium 900	
		38	19	BD type I	Lithium 600–900	0.40 (–5 days)[d]	NA	38	4,045/M	9/9	Lithium 900	
		39	28	BD type I factor V Leiden	Lithium + others[c]	0.85(–180 days)[d]	NA	38	3,501/F	N/K	Lithium 1,500 alt 1,200	
Frew, 2015/USA	Case report N = 1	40	34	BD type I	Lithium 600–900 TM 2–3	NA	NA	Full term	NA	NA	Lithium 600 + others[e]	Exclusive

ALT, alternate; BD, bipolar disorder; D, delivery; F, female; M, male; MP, mother plasma; NA, not available; NK, not known; RDD, recurrent depressive disorder; TM, trimester; UC, umbilical cord; WK, week.

[a]Excluded case: did not meet inclusion criteria of the review; [b]Estimated data through the graph; [c]Medication other than lithium during pregnancy: C_3: chlorthalidone 50 mg every three days for the last four months of pregnancy, thyroglobulin 90 mg/day, secobarbital 30 mg/day occasionally, chloramphenicol and iodochlorhydroxyquin during the second trimester; C_{36}: Bupropion 300 mg, Levothyroxine 50 µg, prenatal vitamins, calcium, fish oil; CN_{37}: Bupropion 300 mg, Levothyroxine 75 µg, prenatal vitamins, fish oil, iron, vitamin D; C_{39}: escitalopram 10 mg, synthroid 25 µg, heparin docusate 200 mg, polyethylene glycol, prenatal vitamines, fish oil, magnesium 800 mg; [d]Day before delivery; [e]Medication other than lithium during postpartum: CN_9: Pethidine HCl 100 + Promazin HCl 50 6 h before delivery; C_{35}: Olanzapine 2.5 mg days 0-15; C_{40}: Quetiapine, Aripiprazol 2.5 two weeks.

Gravidity-Parity Index Case: CN3: G2P2; CN 9: G1P0; CN 36: G2P1; CN 37: G3P2; CN 38: G1P0; CN39: G3P0; CN 40: G2P2.

TABLE 2 | Data of simultaneous monitorization of lithium concentration in mother (serum and/or breast milk) and infant (serum) during breastfeeding and infant outcomes.

Author, year	Mother–infant pair code	Infant age at sampling (week+days)	Maternal weight (Kg)	Maternal lithium dose (mg/day)	[Li] (mEq/L) serum/breast milk			Pharmacokinetic parameters				Infant adverse effects/duration breastfeeding
					Mother (P) N = 56	Breast milk (M) N = 29	Infant (I) N = 58	M/P ratio N = 28	RID (%) N = 23	I/M ratio N = 25	I/P ratio N = 47	
Weinstein and Goldfield, 1969	1	2+3	NA	1,000	0.84	NA	0.04	–	–	–	0.04	None/NA
		10	NA	1,000	0.50	0.12	NA	0.24	–	–	–	
Fries, 1970	2	1	NA	900	0.90	0.30	0.30	0.33	–	1	0.33	None/NA
Tunnessen and Hertz, 1972		0+5	NA	NA	1.5	0.60	0.60	0.40	–	1	0.40	Transient lithium toxicity. The baby was normal by day 8/stop at 5 day
	3	1	NA	NA	NA	NA	0.21	–	–	–	–	
Schou and Amdisen, 1973	4	1	NA	NA	0.34	0.16	0.22	0.47	–	1.37	0.65	NA/NA
	5	2	NA	NA	0.90	0.30	0.30	0.33	–	1	0.33	NA/NA
	6	2	NA	NA	0.84	0.56	0.15	0.66	–	0.27	0.17	NA/NA
	7	3[c]	NA	NA	0.57	0.24	NA	0.42	–	–	–	NA/NA
	8	4	NA	NA	NA	0.50	0.10	–	–	0.20	–	NA/NA
Sykes et al., 1976	9	0+6	NA	400	0.35	0.20	0.03	0.57	–	0.15	0.08	Mildly hypotonic for the first 2 days. Over 63 days showed no negative effects/started within 6 days and stop on week 10
		1	NA	400	0.27	0.14	0.09	0.51	–	0.64	0.33	
		2	NA	600	0.69	0.27	0.06	0.39	–	0.22	0.08	
		4	NA	800	0.95	0.69	0.12	0.72	–	0.17	0.12	
		6	NA	800	1.10	0.27	0.10	0.24	–	0.37	0.09	
		9	NA	800	0.89	0.25	0.09	0.28	–	0.36	0.10	
Skausing and Shou, 1977	10	8	NA	NA	0.70	NA	1.40	–	–	–	2.00	Upper respiratory infection and probably dehydration of 2 months. Lithium toxicity recovered after stop breastfeeding/stop 2 months
Montgomery, 1997	11	2	NA	900	0.62	–	0.31	–			0.50	None. Neurobehavioral and thyroid normal/NA
		4	NA	–	–	–	0.29	–	–	–	–	
Moretti et al., 2003	12	0+1	65.9	600	NA	NA	NA	–	3.50	–	–	None/NA
		0+2	65.9	600	NA	NA	NA	–	3.50	–	–	
		0+4	65.9	900	NA	NA	NA	–	19.90	–	–	
		2	65.9	900	NA	NA	NA	–	19.90	–	–	
	13	2	60	600	NA	NA	NA	–	5.50	–	–	NA/NA
	14	0+5	84	1,500	0.70–0.80	NA	0.14	–	21	–	0.20–0.17	None/NA
		8	84	1,500	0.90	NA	0.22	–	30	–	0.24	
	15	3	NA	900	NA	NA	NA	–	15.50	–	–	None/NA
		3+2	NA	900	NA	NA	NA	–	15.50	–	–	
	16	0+2	67	900	NA	NA	NA	–	24.70	–	–	None/NA
		0+3	67	900	NA	NA	NA	–	15	–	–	
		1+4	67	900	NA	NA	NA	–	25	–	–	
		3+4	67	900	0.47	NA	0.47	–	–	–	1	
	17	1+2	83	600	NA	NA	NA	–	f	–	–	None/NA
		6	83	600	NA	NA	NA	–	f	–	–	
		32	83	600	NA	NA	NA	–	f	–	–	
	18	0	90	600	NA	NA	0.43	–	–	–	–	None/NA
		0+5	90	600	NA	NA	NA	–	15.00	–	–	
		3	90	600	NA	NA	NA	–	6.50	–	–	
	19	2+3	73	1,125	NA	NA	NA	–	6.80	–	–	Neonatal complication no before breastfeeding began/NA

(Continued)

TABLE 2 | Continued

Author, year	Mother–infant pair code	Infant age at sampling (week+days)	Maternal weight (Kg)	Maternal lithium dose (mg/day)	[Li] (mEq/L) serum/breast milk			Pharmacokinetic parameters				Infant adverse effects/duration breastfeeding
					Mother (P) N = 56	Breast milk (M) N = 29	Infant (I) N = 58	M/P ratio N = 28	RID (%) N = 23	I/M ratio N = 25	I/P ratio N = 47	
	20	0	85	1,500	0.58	NA	NA	–	–	–	–	None/NA
		1+2	85	1,500	NA	NA	NA	–	15.70	–	–	
		4	85	1,500	1.34	NA	NA	–	–	–	–	
		5+4	85	1,500	NA	NA	NA	–	23.00	–	–	
	21	0+2	60	1,200	NA	NA	NA	–	8.20	–	–	None/NA
		12	60	1,200	NA	NA	NA	–	5.50	–	–	
	22	>60	130	600	NA	NA	NA	–	<5.00	–	–	None. Lithium started at 15 months /NA
Viguera et al., 2007	23	7	NA	600	0.43	0.30	0.10	0.70	–	0.33	0.23	None/NA
	24	10	NA	600	0.70	0.28	0.20	0.40	–	0.28	0.28	None/NA
		21	NA	600	0.70	NA	0.22	–	–	–	0.31	
		52	NA	600	0.60	0.10	0.10	0.17	–	1	0.17	
	25	1	NA	625	0.80	NA	0.30	–	–	–	0.37	Urea nitrogen 19 mg/dl, creatinine 0.6 mg/dl. No clinical signs of hypovolemia.
		8	NA	625	0.70	NA	0.30	–	–	–	0.42	
		14	NA	625	0.70	NA	0.30	–	–	–	0.42	Normal 1 year later/NA
		24	NA	725	0.60	0.44	0.10	0.73	–	0.17	0.16	
		30	NA	725	0.60	NA	NA	–	–	–	–	
		55	NA	750	0.70	0.46	NA	0.66	–	–	–	
	26	32	NA	700	0.60	0.36	0.09	0.60	–	0.25	0.15	None/NA
	27	4	NA	900	0.90	0.39	0.30	0.43	–	0.77	0.33	None/NA
		12	NA	900	1.00	0.25	0.10	0.25	–	0.40	0.10	
	28	7	NA	900	0.41	0.25	0.23	0.61	–	0.92	0.56	TSH 7.1 μU/ml; TSH 2.07 μU/ml after stop lithium[g]/NA
	29	2	NA	900	0.80	NA	0.10	–	–	–	0.12	Urea nitrogen 22 mg/d. No clinical signs of hypovolemia. Normal 1 year later/NA
		5	NA	900	0.80	0.51	0.13	0.64	–	0.25	0.16	
		14	NA	900	0.92	0.40	0.10	0.43	–	0.25	0.10	
		32	NA	900	0.92	NA	0.20	–	–	–	0.21	
		52	NA	900	NA	NA	0.10	–	–	–	–	
	30	8	NA	900	1.31	NA	0.14	–	–	–	0.11	None/NA
	31	6	NA	1,200	1.16	0.48	0.19	0.41	–	0.40	0.16	None/NA
		25	NA	1,200	1.03	NA	0.05	–	–	–	0.04	
	32	4	NA	1,200	0.55	0.37	0.10	0.67	–	0.27	0.18	None/NA
		10	NA	1,200	0.55	NA	0.10	–	–	–	0.18	
		14	NA	1,200	0.67	0.40	0.18	0.60	–	0.27	0.26	
		25	NA	1,200	0.65	NA	0.14	–	–	–	0.21	
Tanaka et al., 2008	33	0+1	NA	1,200	0.41	0.44	4.19[e]	1.07	–	–	–	Spurious toxic infant lithium level suspected. Tube feeding and mother´s milk start on day 7
		0+4	NA	1,200	NA	NA	0.11	–	–	–	–	
		0+6	NA	1,200	NA	NA	<0.10	–	–	–	–	
		1+3	NA	1,200	NA	NA	<0.10	–	–	–	–	
	34[b]	0+3	NA	NA	NA	NA	<0.30	–	–	–	–	Spurious toxic infant lithium level suspected. None.
		0+6	NA	NA	NA	NA	0.70	–	–	–	–	NA
		1+3	NA	NA	NA	NA	1.10	–	–	–	–	
		1+4	NA	NA	0.70	NA	NA	–	–	–	–	
		2+4	NA	NA	NA	NA	1.10	–	–	–	–	

(Continued)

TABLE 2 | Continued

Author, year	Mother–infant pair code	Infant age at sampling (week+days)	Maternal weight (Kg)	Maternal lithium dose (mg/day)	[Li] (mEq/L) serum/breast milk			Pharmacokinetic parameters				Infant adverse effects/duration breastfeeding
					Mother (P) N = 56	Breast milk (M) N = 29	Infant (I) N = 58	M/P ratio N = 28	RID (%) N = 23	I/M ratio N = 25	I/P ratio N = 47	
Marín et al., 2011	35	2+1	NA	800	0.74	NA	0.26	–	–	–	0.35	TSH (μU/ml): 5.14 at 1 month; 3.55 at 2 months; 2.17 at 6 months. No electrolyte or liver abnormalities.
		4	NA	800	NA	NA	0.23	–	–	–	–	
		8	NA	800	NA	NA	0.23	–	–	–	–	Normal neurodevelopment at 6 months/NA
		24	NA	800	NA	NA	0.17w	–	–	–	–	
Bogen et al., 2012	36	4+3	NA	900	0.72	NA	0.08	–	–	–	0.11	Weight loss (4.2% day 2, 5.9% day 7). Feeding problems. Mild hypotonia (2 months). Early intervention care for gross and fine motor delay through the first year/duration past 1 year
		26+1	NA	900	0.48	NA	0.08	–	–	–	0.17	
	37	6+1	NA	900	0.73	NA	0.11	–	–	–	0.15	None/NA
	38	0+4	NA	900	0.78	NA	NA	–	–	–	–	Weight loss (5.2% day 2 and 8.5% day 3).
		6+3	NA	900	0.81	NA	0.08	–	–	–	0.10	Feeding problems. 4 months
	39	2	NA	1,350 [d]	0.12	NA	NA	–	–	–	–	None/7 months
		4+3	NA	1,350 [d]	0.97	NA	0.11	–	–	–	0.11	
Frew, 2015	40	1+3	NA	600	0.45	NA	0.26	–	–	–	0.58	None/NA
	Mean (SD) range	8.61 (12.98) [0–60]		904.2 (283.2) [400–1,500]	0.73 (0.3) [0.12–1.50]	0.34 (0–14) [0.10–0.69]	0.23 (0.26) [0.03–1.40]	0.49 (0.19) [0.17–1.07]	12.12 (8.5) [0–30]	0.49 (0.35) [0.15–1.37]	0.28 (0.31) [0.04–2.00]	8 over 39 (21%)

NA, not available. [a]Estimated data through the graph; [b]Excluded case: did not meet inclusion criteria; [c]Mean determinations of five consecutive days; [d]Patient took 1,500 mg every other day alternating with 1,200 every other day; [e]False elevation of blood lithium levels caused by contamination in a lithium heparin container commented by the author. [f]Undetectable. [g]Normal thyroid-stimulating hormone (TSH) range: 1-30-day-old infants: 0.52-16.00 μU/ml; 1-month to 5-year-old-children: 0.55-7.10 μU/ml (Siparsky and Accurso, 2007).

Infant-Plasma Lithium Concentration (I)

The mean infant plasma/serum lithium concentration was 0.23 (0.26) mEq/L (0.03–1.40).

Milk-to-Maternal Plasma Lithium Concentration Ratio (M/P Ratio)

The mean breast milk lithium concentration was 0.34 (0.14) mEq/L (0.10–0.69). The milk-to-maternal serum lithium ratio (M/P) was calculated in 28 samples. The average M/P ratio was 0.49 (0.19) (0.17–1.07). These data were obtained from a single time point.

Relative Infant Dose (RID)

Moretti et al. (2003)'s study was the only one to report the RID in infants exposed to lithium. The mean RID value was 12.2% (8.5%) (0–30%; median 11.2%; 95% CI, 6.3 to 18.0%); however, 11 of the 23 samples had a RID value between 10 and 25%, and 1 above 25%.

Infant-Plasma-to-Maternal Plasma Lithium Concentration Ratio (I/P Ratio)

The mean I/P ratio was 0.28 (0.31) (0.04–2.00). The I/P ratio was obtained from 47 samples.

Finally, Viguera et al. (2007) have described in her study a different index called the Infant-plasma-to milk lithium concentration ratio (I/M). The mean I/M ratio was 0.49 (0.35) (0.15-1.37).

Clinical Adverse Effects in Breastfed Infants

Of the 39 breastfed infants included in this review, 8 (20.5%) showed a clinical adverse event. Two had transient lithium toxicity that recovered after discontinuation of breastfeeding (Tunnessen and Hertz, 1972; Skausing and Shou, 1977). Two cases had mild hypotonia, one for the first 2 days of life (Sykes et al., 1976), and the other after 2 months (Bogen et al., 2012). Finally, two cases of weight loss in the first week were recorded (Bogen et al., 2012), and one case with transient hypothyroid (increased TSH) and two cases with renal parameter alterations (increased creatinine and/or urea nitrogen parameters) (Viguera et al., 2007). Moreover, 2 of the 39 breastfed infants had congenital malformations (a congenital heart disease which underwent surgery on postpartum day 3 (Tanaka et al., 2008), and one hypospadias and right cryptorchidism (Marín et al., 2011) not related to the transfer of lithium during lactation. The case with congenital heart disease was initially suspected of having an acute transient lithium intoxication; however, authors explained that it was a false elevation of infant lithemia due to a contamination of lithium, heparin container. Finally, it must be said that four infants were exposed prenatally to lithium polytherapy (Tunnessen and Hertz, 1972; Bogen et al., 2012), and three during lactation (Sykes et al., 1976; Marín et al., 2011; Frew, 2015) (see **Tables 1** and **2**).

Quality Assessment

Table 3 shows the results of the quality assessment. Only 2 studies of the 13 included (15%) in the systematic review complied with 50% or higher of the quality check list items.

All studies except Moretti et al. (2003) had a mother–infant pair design (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen

TABLE 3 | Quality checklist of clinical lactation studies of the included studies based upon the ILCA, FDA, and EMA guidelines.

Author year	Weinstein and Goldfield, 1969	Fries, 1970	Tunnessen and Hertz, 1972	Schou and Amdisen, 1973	Sykes et al., 1976	Skausing and Shou, 1977	Montgomery, 1997	Moretti et al., 2003	Viguera et al., 2007	Tanaka et al., 2008	Marín et al., 2011	Bogen et al., 2012	Frew, 2015	
Study design														
Mother–infant pair design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes 2/11	Yes	Yes	Yes	Yes	Yes	100%
Other consideration: longitudinal	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	38%
Monotherapy/polytherapy	NA	NA	Yes	No	Yes	NA	NA	NA	Yes	NA	Yes	Yes	Yes	46%
Clinical conduct														
Clear sampling strategy	No	No	No	No	No	No	No	No	No	No	No	No	No	0%
Lithium dose	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	85%
Lithium frequency	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
Steady state	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
Time of drug intake until sampling	NA	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA	7%
Sampling at least in two of three matrices[a]	Yes	Yes	Yes	Yes 3/5	Yes	Yes	Yes	Yes 2/11	Yes 9/10	Yes	Yes	Yes	Yes	100%
Sampling assessed simultaneously	NA	NA	NA	NA	Yes	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	46%
Pharmacokinetic endpoints														
Infant plasma/serum concentration	Yes	Yes	Yes	Yes 4/5	Yes	Yes	Yes	Yes 3/11	Yes	Yes	Yes	Yes	Yes	100%
Milk/plasma/serum ratio	Yes	Yes	Yes	Yes 4/5	Yes	No	No	No	Yes	Yes 1/2	No	No	No	54%
RID	NA	NA	NA	NA	NA	NA	NA	Yes 9/11	NA	NA	NA	NA	NA	7%
I/P ratio	Yes	Yes	Yes	Yes 3/5	Yes	Yes	Yes	Yes 2/11	Yes	No	Yes	Yes	Yes	92%
Infant clinical monitorization														
Adverse effect evaluated	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	92%
Use of pediatric rating scale/systematic clinical evaluation	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
Laboratory methods[b]														
Methods description	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
Separate milk validation report	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA	NA	7%
Assay sensitivity reported	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	NA	7%
Detection methods used reported	NA	NA	NA	Yes	NA	NA	NA	NA	Yes	NA	NA	Yes	NA	23%
Total quality percentage of items (%)	35%	35%	40%	30%	45%	25%	30%	45% [c]	60%	35%	45%	55%	45%	

I/P ratio, infant to maternal plasma/serum lithium concentration ratio; M/P ratio, milk-to-maternal plasma ratio; NA, not available; RID, relative infant dose. [a]Matrices: Maternal plasma/serum, milk, infant plasma/serum. [b]Laboratory Technique: Schou and Amdisen (1973) Flame photometric method; Viguera et al. (2007) Lithium concentration in maternal and infant sera by standard commercial laboratory methods. Lithium concentration in breast milk by ion-selective electrode detection (Beckman Coulter, Fullerton, Calif.); Tanaka et al. (2008) ion especific electrode method on the Roche Integra 400 Analizer; Bogen et al. (2012) Inductively coupled plasma-mass spectrometry (quality control CVs of 4.0% to 7.0% at target levels of 0.025 and 1.800 meq/L with a lower limit of 0.01 meq/L. [c]Moretti et al. (2003) partially complies with 45% of the items (3/11).

and Hertz, 1972; Schou and Amdisen, 1973; Sykes et al., 1976; Skausing and Shou, 1977; Montgomery, 1997; Viguera et al., 2007; Tanaka et al., 2008; Marín et al., 2011; Bogen et al., 2012; Frew, 2015). Moretti et al. (2003) used a mixed design: in two cases, a mother–infant pair, and in nine cases, a lactating-women-milk-only design. Five studies had a longitudinal design (Moretti et al., 2003; Viguera et al., 2007; Marín et al., 2011; Bogen et al., 2012; Frew, 2015). As all studies included in the review were case reports or case series applying a clinical approach, none had a clear strategy for sample extraction. The maternal lithium dose during lactation was reported in 10 studies (Weinstein and Goldfield, 1969; Fries, 1970; Sykes et al., 1976; Moretti et al., 2003; Viguera et al., 2007; Tanaka et al., 2008; Marín et al., 2011; Bogen et al., 2012; Frew, 2015). No information on the frequency of lithium prescription and time of lithium intake until sampling was available in any of the studies. Seven out of the 13 studies had samples from all 3 matrices (mother and infant plasma/serum and milk) (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen and Hertz, 1972; Schou and Amdisen, 1973; Sykes et al., 1976; Viguera et al., 2007; Tanaka et al., 2008). Only one study stated specifically that sampling was obtained simultaneously in the three matrices (Viguera et al., 2007). Finally, none of the studies reported that sampling was taken in steady state.

With respect to pharmacokinetic end-points assessed, *the infant-plasma-lithium concentration (I)* was obtained in almost all cases (58 samples; 38/39 cases). Only 1 study (Viguera et al., 2007) assessed *the milk-to-mother plasma ratio (M/P)* in 10 women, but 6 more studies provided data for calculating this ratio (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen and Hertz, 1972; Schou and Amdisen, 1973, Sykes et al., 1976; Tanaka et al., 2008). In all cases, the M/P ratio was obtained from a single time point. The *RID* was calculated only in 1 study of the 13 (Moretti et al., 2003). In 7 of the 11 cases, milk was obtained from multiple samples at a specific dose interval. Finally, *the infant-plasma-to mother-plasma ratio (I/P ratio)* was studied in 12 studies (Weinstein and Goldfield, 1969; Fries, 1970; Tunnessen and Hertz, 1972; Schou and Amdisen, 1973; Sykes et al., 1976; Skausing and Shou, 1977; Montgomery, 1997; Moretti et al., 2003; Viguera et al., 2007; Marín et al., 2011; Bogen et al., 2012; Frew, 2015). Only four studies provided partial information on the laboratory methods used in the lithium measurement in plasma/serum and milk (Schou and Amdisen, 1973; Moretti et al., 2003; Viguera et al., 2007; Bogen et al., 2012).

Of the 13 studies, only 1 (Schou and Amdisen, 1973) did not report short-term infant adverse effects during lactation.

DISCUSSION

Breastfeeding is known to have clear general health benefits for mother and infant (WHO, 2017). However, delivery is a situation of biological and psychosocial stress, especially for vulnerable women (Sanjuan et al., 2008). Postpartum is a high-risk period for the initiation or recurrence of affective disorders (Munk-Olsen et al., 2009; Bergink et al., 2012). In recent years, interest has increased in supporting breastfeeding in women who may benefit from initiating or maintaining psychopharmacological treatment in the postpartum period. Lithium is considered a first-line treatment in bipolar disorder in most international guidelines (Malhi et al., 2017). In this systematic review, we assessed the current evidence and quality of studies that have evaluated lithium transfer to lactating infants, and their short-term outcomes.

This systematic review included data from 13 highly heterogeneous studies (39 cases); all of them case are reports or case series. The cases were informative, but the absence of a standard protocol makes interpretation difficult (Wang et al., 2017). This review is not without limitations. The search was restricted to PubMed and LactMed databases and to English and Spanish language peer-reviewed journals, and potentially we could miss studies published in other languages or in specific journals. The sample size, the degree of level of evidence, and quality of studies included were all less than optimal. Fewer than 16% of studies applied more than 50% of quality check-list items (see **Table 3**).

First of all, some of the studies included failed to report important variables that may have affected lithium concentration during lactation (**Table 1**): maternal factors (ethnicity, age, gravity/parity, weight, clinical diagnosis), pharmacokinetic factors [diet, smoking, alcohol intake, concomitant medication (i.e., non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, or diuretics as they may increase lithium concentration)] or other medical conditions (hyperemesis gravidarum, thyroid and renal illness, polyhydramnios, preeclampsia), and infant factors such as age (as we note above), term/preterm birth, and extended breastfeeding.

All studies included had a mother–infant pair design, but few were longitudinal. There were variations between maternal lithium dose and plasma/serum concentrations in mother, milk and infants, and also over the lactation period. We sought to establish whether there was a correlation between maternal and infant lithemia during the first week, but found very few data for this period (see **Table 2**). Moreover, as the majority of women had also been treated with lithium during late pregnancy, one might think that these initial infant lithemias were influenced more by placenta transfer than by lactation transfer. The milk-to-maternal plasma ratio (M/P) was below 1 in almost all cases (17/18). This indicated that lithium milk concentration was not superior to maternal concentration (i.e., there was no accumulation). With respect to the RID, studied only by Moretti et al. (2003), the results indicated that lithium can be used with caution during lactation. Although the RID is a well accepted measure of the safety of medication use during breastfeeding, as we noted above, it has substantial limitations (e.g., it does not take into account the age of the infant) [Anderson and Sauberan, 2016].

The pharmacokinetic parameter that provided the most information on infant safety was probably the infant-plasma concentration (Anderson and Sauberan, 2016). In the majority of the cases reviewed, the results were below 0.30 mEq/L, and no adverse effects were seen. However, six cases (Tunnessen and Hertz, 1972; Skausing and Shou, 1977; Montgomery, 1997; Moretti et al., 2003; Tanaka et al., 2008) showed higher lithemias (see **Table 2**). In the first case described by Tunnessen and Hertz, 1972, the infant developed cyanosis, hypothermia, hypotonia, and heart murmur within a few hours of birth. Infant lithemia was determined at 5 days of life when she experienced a cyanotic episode. At that time,

the mother had a serum lithium concentration of 1.5 mEq/L, and the breast milk and the infant serum levels were 0.6 meq/L. The infant's levels were completely normal by day 8. Her mother had taken lithium throughout pregnancy and the long-acting diuretic chlorthalidone prior to delivery, showing an increased lithemia (1.07–1.38 mEq/L). Since maternal and fetal lithium concentration are equal in utero, this intoxication might be due to a combination of maternal dose transfer and the slow renal excretion by the infant. It is known that levels of lithium clearance within the first days of delivery are a third of adult values after adjusting for differences in body surface area, but by the age of 6 months, this difference disappears (Lu and Rosembaum, 2014).

The second case, of Skausing and Shou (1977), was an infant who had been breastfeeding for 2 months without adverse effects, with an I/P ratio of 50%. At 2 months of life, after a respiratory infection and probably secondary dehydration, the infant showed signs of toxicity. Serum lithium levels were 1.4 mEq/L in the infant and 0.7 mEq/L in the mother, and the I/P ratio was 200%. The intoxication remitted after discontinuation of breastfeeding.

In the case reported by Tanaka et al. (2008) (see **Table 1**, case 33), the authors suspected that the toxic infant lithium level (4.19 meq/L) was spurious because of the absence of clinical symptoms of toxicity in the infant. Moreover, the other three cases with lithemia > than 0.30 mEq/L (Montgomery, 1997; Moretti et al., 2003) were not associated with adverse events. On the other hand, we found three cases with transient thyroid or renal parameters alterations in infants with lithemias between 0.23 and 0.10 mEq/L (Viguera et al., 2007). Lastly, there were two cases with weight loss in the first week of life with lithemias between 0.17 and 0.10 mEq/L published by Bogen et al. (2012). However, both cases were under polytherapy during pregnancy (antidepressant and lithium). These infants were born at term with adequate weight for gestational age, and both regained weight at 21 and 4 days, respectively, with breastfeeding support (Bogen et al., 2012). It seems that one of the most important variables for safety is infant age, related to changes in absorption, distribution, and excretion (Lu and Rosembaum, 2014). In this regard, adverse drug reactions occur in the first 2 months of life in close to 80% of cases exposed to drugs during lactation (Anderson et al., 2003; Soussan et al., 2014; Anderson et al., 2016). A similar figure was observed in the present review with lithium, supporting our results.

CONCLUSIONS

The current information on lithium use during breastfeeding is based on a small and heterogeneous number of case reports and case series which have used different pharmacokinetic parameters of varying clinical relevance to estimate the short-term risk of lithium in nursing infants. In the studies included, 20% of infants presented transient short-term adverse effects.

The results of the review help us to identify several areas for improvement in future clinical research into lithium and lactation. Studies should include prospective longitudinal samples, recording a range of variables: socio-demographic, clinical (psychiatric, obstetric, and neonatal), therapeutic, and analytical; groups should be homogeneous (i.e., receiving monotherapy and/or polytherapy, with prenatal and/or postnatal lithium exposure); blood samples should be obtained simultaneously from mother–infant pairs, at several time points relative to delivery; useful pharmacokinetic parameters should be evaluated with validated laboratory methods; and a standardized clinical pediatric assessment of infants should be performed during lactation.

Based on the results of the systematic review, in the case of a woman who is reacting well to lithium therapy in the early postpartum period and chooses maternal lactation, we make the following recommendations:

- Multidisciplinary management in collaboration with obstetricians, pediatricians, toxicologists, and psychiatrists
- Prenatal discussion with the mother regarding the risk and benefits of breastfeeding with and without lithium
- In women treated with lithium during late pregnancy, monitoring and analysis of lithium levels in the mother–infant pair during delivery, at 48h postpartum and 10 days postpartum
- In women who initiate lithium treatment in postpartum, monitoring and analysis of lithium levels in the mother–infant pair at 10 days after starting treatment. Infant analysis should include thyroid and renal parameters.
- If infant lithemia is <0.30 mEq/L, lithemia monitoring should only continue in the mother–infant pair if there are clinical symptoms of lithium intoxication.
- Clinical monitoring of the infant should include weight gain, in addition to neurodevelopment. The mother should be referred to a breastfeeding support group or to an early intervention service if needed. Psychoeducation should be provided for parents or caregivers to monitor their infants for signs and symptoms of feeding problems, dehydration, hypotonia, and lethargy.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Case study concept and design: MI and RM-S. Acquisition, analysis, or interpretation of data: MI, MT and RM-S. Drafting of the manuscript: MI and RM-S. Critical revision of the manuscript for important intellectual content: All authors. Technical, or material support: MI and MT.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2019.01005/full#supplementary-material

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6 HIPÓTESIS

GENERAL

1. Los cambios renales fisiológicos y las complicaciones obstétricas asociadas con el embarazo y el tipo de lactancia materna serán responsables de los cambios farmacocinéticas del litio en la madre que a su vez pueden afectar la eficacia clínica y la toxicidad del litio materna y neonatal.

ESPECÍFICAS

1. Los cambios fisiológicos de la función renal y las complicaciones obstétricas asociadas con el embarazo alterarán la farmacocinética del litio pudiendo afectar la eficacia y seguridad terapéutica en la madre.
2. Una breve discontinuación periparto del tratamiento con litio, se asociará a pequeñas fluctuaciones de la litemia materna que no comprometerán su eficacia minimizando el riesgo de toxicidad materna y neonatal.
3. La transferencia placentaria de litio será superior que la transferencia a través de la leche materna en mujeres en tratamiento con litio.
4. Los lactantes expuestos a litio intraútero y a través de la leche materna no presentarán acumulación de litio.

7 OBJETIVOS

OBJETIVO GENERAL

1 Caracterizar el comportamiento del litio en el periodo perinatal y su impacto clínico y analítico sobre la diada madre-hijo que genere nuevo conocimiento científico para la ayuda en la toma de decisiones compartidas eficaces y seguras.

OBJETIVOS ESPECÍFICOS

1. Caracterizar los cambios en la disposición del litio en el periodo perinatal (preconcepción, embarazo y primer año posparto) y su relación con la función renal durante el embarazo y el posparto.

2. Estudiar el impacto de los cambios fisiológicos y patológicos en las concentraciones de litio durante el embarazo sobre la eficacia clínica y toxicidad materna.

3. Estudiar los cambios en las concentraciones séricas de litio materno en el periodo periparto (desde el ingreso hospitalario para el parto hasta los primeros 7 días posparto) tras una breve discontinuación del tratamiento con litio (al ingreso para el parto hasta 6-12 horas posparto).

4. Estudiar la transferencia transplacentaria de litio en el momento del parto, correlacionando la concentración del litio del cordón umbilical con la materna.

5. Estudiar la asociación entre la litemia neonatal (cordón umbilical o primer día posparto) y los resultados neonatales agudos.

6. Estudiar el comportamiento de las concentraciones de litio en la diada madre neonato/lactante expuesta a litio en monoterapia durante el tercer trimestre del embarazo y la lactancia materna exclusiva.

7. Estudiar el comportamiento de las concentraciones de litio neonatal/lactante en función de las diferentes trayectorias de alimentación (lactancia maternal exclusiva, mixta o artificial) de madres en tratamiento continuado con litio en la etapa perinatal.

8 MATERIAL, MÉTODOS Y RESULTADOS

8.1 Artículo 1: resumen estructurado

Imaz ML, Torra M, Langohr K, Poch E, Soy D, García-Esteve L, Vieta E, Martin-Santos R. How does pregnancy affect drug disposition of lithium? A retrospective observational cohort study. Sometido a revisión

Antecedentes: El litio se considera el estándar de oro para el tratamiento del trastorno bipolar durante el período perinatal tanto para la madre como para el feto/neonato en comparación con otras opciones de tratamiento de mantenimiento. El litio se excreta principalmente por vía renal y los cambios fisiológicos del embarazo renal pueden afectar su farmacocinética.

Objetivo: Caracterizar los cambios en la disposición de litio en el período perinatal y su relación con la función renal durante el embarazo y el posparto.

Método: Estudio observacional, de cohortes, retrospectivo (noviembre 2006-diciembre 2018). Se obtuvieron datos de las litemias (N=1260) y creatininemia (N=1326) de 109 embarazos de la historia clínica de 95 mujeres tratadas con litio durante el período perinatal. Se estudió el patrón longitudinal de las concentraciones séricas de litio y creatinina y de la ratio litemia/dosis, mediante modelos lineales mixtos. La prueba de probabilidad logarítmica restringida mostró la bondad de ajuste de los modelos. Se evaluó la asociación lineal entre la creatininemia y la litemia y la relación concentración/dosis de litio mediante el coeficiente de correlación de Pearson.

Resultados: La litemia media fue estimada como un modelo mixto incluyendo la dosis de litio y el tiempo como predictores. Para una dosis de 1000 mg, la concentración disminuyó un promedio del 30,2% (IC95%=25,2%-35,4%) en el primer trimestre, 29,7% (25,2%-34%) en el segundo, 20,6% (16,4%-23,7%) en el tercero, y aumentó un 2,4% (-1,7%-7,1%) y 0,3% (-4,6%-5,6%) en el primero y segundo-cuarto trimestre posparto. La creatinina exhibió un patrón longitudinal similar al observado de la litemia durante el embarazo y posparto. Las medidas repetidas de correlación durante el embarazo y el posparto fueron estadísticamente significativas ($p<0,05$).

Conclusiones: La monitorización de la litemia es fundamental antes y durante el embarazo, así como en el puerperio, para asegurar una dosis adecuada. Se recomienda monitorizar el clearance renal del litio a través de las concentraciones séricas de creatinina, así como monitorizar mensualmente la litemia hasta la semana 30 de embarazo, y a partir de ahí de forma semanal hasta el parto y bisemanal durante el primer mes posparto.

TITLE:

How does pregnancy affect lithium disposition? A retrospective observational cohort study.

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ABSTRACT

Background: Lithium is considered the gold standard for the treatment of bipolar disorder during the perinatal period for both mother and fetus/neonate compared with other maintenance treatment options. Lithium is mainly excreted by kidney and renal pregnancy physiological changes may affect its pharmacokinetic.

Aims: To characterize the changes in lithium disposition in the perinatal period, and to study whether changes in litemia are related to renal function during pregnancy and postpartum.

Methods: Retrospective observational cohort study (November 2006-December 2018). Data on lithium (N=1260) and creatinine (N=1326) serum concentration measurements obtained from 109 pregnancies of 95 women treated with lithium during perinatal period, were collected from clinical records. Longitudinal pattern of serum lithium and creatinine concentrations during perinatal period were studied using linear mixed models. Pearson's correlation coefficient was used to assess linear associations between serum creatinine concentration and serum lithium concentration during the perinatal period.

Results: Mean lithium concentrations were estimated with a mixed model including time and lithium dose as predictors. Given a dose of 1000 mg, concentrations decrease on average 30.2% (95%CI: 25.2%, 35.4%) in the first trimester, 29.7% (25.2%, 34%) in the second, 20.6% (16.4%, 23.7%) in the third, and increase by 2.4% (-1.7%,7.1%) and 0.3% (-4.6%.5.6%) in first and second-fourth postpartum trimester. Serum creatinine concentrations evidenced a similar longitudinal pattern during pregnancy and postpartum. Repeated measures correlation was statistically significant ($p < 0.05$) during pregnancy and postpartum.

Conclusions: Serum lithium concentration monitoring is essential prior to and during pregnancy as well as postpartum to ensure adequate dosing. Serum creatinine concentrations measurement is recommended to monitor lithium renal clearance. We suggest close monitoring the litemia until 30 weeks of pregnancy, then weekly until delivery and (bi-) weekly for the first month postpartum.

Key words: lithium; creatinine; preconception; pregnancy; postpartum; therapeutic drug monitoring.

1. Introduction

Lithium is considered by many authors the gold standard for the treatment of bipolar disorder during pregnancy and postpartum. Compared with other maintenance treatment options, lithium offers the best efficacy/safety ratio for both mother and fetus/neonate. Lithium use during the first trimester of pregnancy is associated with a dose dependent increased risk of congenital malformations, although with a smaller magnitude effect than early postulated (Patorno et al., 2017). Meanwhile other pharmacological options (i.e. valproate and carbamazepine) are known teratogenic agents (Larsen et al., 2015; Vajda et al., 2023). Lithium is proven effective as maintenance treatment for bipolar disorder and to prevent postpartum psychosis (Bergink et al., 2012; Wesseloo et al., 2016) than others (such as lamotrigine or antipsychotics) less efficient (Bergink et al., 2014; Cohen et al., 2016; Larsen et al., 2015). Maintained lithium use during pregnancy might represent the best risk–benefit option, especially for women stabilized with lithium before pregnancy.

Lithium is a free cation that is completely absorbed in the gastrointestinal tract and is not metabolized. Excretion of lithium is almost exclusively renal, hence serum concentrations mainly depend on intravascular volume and glomerular filtration rate (GRF) (Grandjean and Aubry, 2009). It is filtered through the glomeruli, and 70-80% is reabsorbed by the proximal tubule. Lithium clearance is usually 20% to 30% of the GFR and thus varies with it (Thomsen and Schou, 1999). No gender or ethnicity-related differences in kinetics have been demonstrated (Grandjean, and Aubry, 2009). Lithium elimination half-life is about 18-24 hours in healthy young subjects. Steady state concentrations are achieved within 4-5 days. Lithium dosages should be adjusted based on the serum concentration drawn, optimally 12 hours after the last dose. The usual maintenance daily dose is 25-35 mmol (lithium carbonate 925-1300 mg) for patients aged <40 years. Lithium has a narrow therapeutic index of 0.6 to 1.2 mEq/L (Hiemke et al., 2017). Lithemias <0.4 mEq/L are likely to be in a subtherapeutic response; and lithemias >1.0 mEq/L increase the risk of toxicity (Clark et al., 2022). The most common optimal serum concentration range for maintenance treatment is 0.50-0.80 mEq/L (Malhi et al., 2017) with the option to reduce it to 0.40-0.60 mEq/L in case of good response but poor tolerance or to increase it to 0.80-1.00 mEq/L in case of insufficient response and good tolerance (Nolen et al., 2019). Patients using lithium are known to have a high intra- and inter-individual variability in dose-concentration relationship. Several factors such as

inconsistent adherence, natrium depletion, dehydration, diet, drug-drug interactions, kidney disease, and obstetrical and delivery complications (e.g. nauseas and vomiting, symptoms of preterm birth, pre-eclampsia or postpartum hemorrhage) can all cause serum lithium concentration changes in addition to pregnancy (Thomsen and Schou, 1999; Clark et al., 2022).

Pregnancy is a complex state, characterized by profound and reversible anatomical and functional renal changes beginning to occur as early as the first trimester of pregnancy, between 6 and 10 weeks of gestation. Compare with pre-pregnancy levels, the renal blood flow (RBF) rises to about 70-80% from its baseline value at 20-22 weeks of gestation, peaks around 32-24 weeks of gestation, and then falls to about 60-70% above pre-pregnancy levels towards the end of pregnancy. The GFR rises in parallel to the RBF about 40-50% of its baseline values at 20-22 weeks, then continues to increase through most of the third trimester up to 36-38 weeks of gestation, when it declines steadily by 15-20% until the time of delivery (Eke, 2022; Eke et al., 2023). The increased RBF and GFR are responsible for the decreased serum creatinine (from a mean 0.70 to 0.40-0.60 mg/dL), and increased protein excretion (up to 300 mg/day) during pregnancy (Eke et al., 2023). Creatinine clearance, a measurable surrogate marker of GFR (Wiles et al., 2018) is a predictor of lithium elimination clearance. Increases in lithium clearance during pregnancy result in reduced serum lithium concentrations. In early postpartum, vascular volume rapidly decreases by approximately 40% and hyperfiltration has been shown to continue at levels of 20% above normal at postpartum week 2 and return to pre-pregnancy levels by 2-10 weeks postpartum (Odutayo and Hadunewich, 2012). Renal changes associated with pregnancy are responsible for alterations in lithium pharmacokinetics that may in turn impact lithium efficacy and toxicity in mother (Pinheiro, 2020).

Our current knowledge on lithium disposition in the perinatal period is limited to few studies. A small early experimental study (Schou et al., 1973) and a more recent prospective study (Clark et al., 2022) reported that lithium elimination clearance doubled in the final trimester compared with non-pregnant state. Data from two retrospective observational studies showed that serum lithium concentrations declined across pregnancy (Westin et al., 2017; Wesseloo et al., 2017) and the largest of them (Wesseloo et al., 2017) have shown that serum lithium concentrations decreased during pregnancy an average of 24% in the first trimester, 36% in second trimester and 21% in the third trimester compared to preconceptional period. Creatinine blood levels showed a similar

longitudinal pattern, showing that indeed changes in serum lithium concentrations reflect changes in renal physiology. During postpartum period lithium still slightly increased an average of 9% (Wesseloo et al., 2017).

Due to the limited lithium pharmacokinetic data available in the perinatal period, recommendations on lithium monitoring and dose adjustment are scarce (Graham et al., 2017). The UK National Institute for Health and Care Excellence (NICE Guidelines CG192, 2014, updated 2020), the Dutch Association for Psychiatry (NVVP Dutch Association, 2014) and the British Association for Psychopharmacology Consensus guidelines (McAllister-Williams et al., 2017), and some authors (Wesseloo et als.,2017) state that where lithium therapy is continued during pregnancy, serum lithium concentrations should be monitored every three-four weeks until the 34th week, then weekly from the 36th week until delivery and adjust the dose to keep serum lithium concentrations in the woman's therapeutic range. To maintain effective serum lithium concentrations during pregnancy, doses generally need to be increased by 50% (Westing et al., 2017; Clark et al., 2022). Because of the high-risk for postpartum relapse (37%) in women with bipolar disorder during the first month postpartum, a high target therapeutic serum lithium concentration (e.g. 0.8-1.0 mEq/L) has been recommended to maximize maternal relapse prevention (Wesseloo et al., 2017).

In this context, aims of the current study were to characterize during the perinatal period the trajectory of lithium disposition, to know which factors may influence lithium concentrations, whether litemia changes are consistent with changes in renal function, and the impact of lithium alterations in his efficacy and toxicity in mother.

2. Methods

A retrospective observational cohort study was conducted in the Perinatal Mental Health Unit (PMHU) of a single university hospital. Data was collected from clinical records from November 2006 to December 2018.

2.1. Participants

We included data from women treated with lithium in monotherapy or polytherapy during the perinatal period (1styear preconception, pregnancy, and 12 months postpartum) with at least one lithium measurement during pregnancy. Preconcepcional stable treated hypothyroidism and/or diabetes mellitus were not an exclusion criteria. Analyses were excluded if: (1) no serum lithium concentration was detected; (2) the sample was not obtained at steady-state condition (minimum 5 days after the lithium dose adjustment); (3) the sample was obtained 12 ± 2 hours after the last intake of lithium dose; or (4) the sample analysis was performed in a laboratory other than the Pharmacology and Toxicology Laboratory at our teaching hospital. Peripartum serum lithium concentration measurements (from admission day for hospital birth to postpartum day 5) were excluded because the samples were not obtained at steady-state condition and/or were obtained <10 hours or >14 hours after the lithium dosing.

2.2. Data collection and procedures

This study was performed in accordance with the STROBE statement for cohort studies (Von Elm, 2007). It included sociodemographic, psychiatric and obstetric data for each woman and her corresponding pregnancies obtained from the hospital medical records. Obstetric complications evaluated included prematurity (birth before 37 complete weeks of gestation), gestational diabetes, gestational hypertension, pre-eclampsia, polyhydramnios and oligohydramnios. The analysis tests included electrolytes (sodium, potassium) kidney function (creatinine), and serum lithium concentration collected in the morning 12±2 hours after the last dosing lithium and under steady-state condition. We monitor mothers every four-weeks until 34 weeks of pregnancy and then weekly until delivery. We also monitor mothers at day 2±1 postpartum, followed by (bi-) weekly during the first month postpartum. Then, monthly until 6 months postpartum and then continue to monitor every 3-4 months. Additionally, we monitored serum lithium concentrations 5-7 days after lithium dose adjustment, and 3-5 days after litemia

values ≥ 1.00 mEq/L or ≤ 0.40 mEq/L. The preconceptional and pregnancy time periods were synchronised between women based upon the estimated gestational age by first trimester ultrasound and the postpartum time period was synchronised based upon delivery. We extracted lithemia measurements during six different perinatal time periods with respect to pregnancy: preconception (52 weeks preceding the estimated date of conception), first trimester pregnancy (0–13 weeks of gestation), second trimester pregnancy (14–26 weeks of gestation), third trimester pregnancy (27–40 weeks of gestation), first trimester postpartum (0-12 weeks postdelivery) and second to fourth trimester postpartum (13-52 weeks postdelivery).

The maternal lithium therapeutic drug monitoring (TDM) database contained information about the prescribed daily lithium dose, lithium dosing changes and dosing frequency, time of last lithium dose intake, time of blood sampling, serum lithium and serum creatinine concentrations and types and doses of concomitant medications. Serum lithium (mEq/L) and serum creatinine (mg/dL) concentrations were reported with two significant digits after the decimal point.

2.3 Serum lithium analysis

For lithium analysis, maternal venous blood samples (5 ml) were collected into Vacutainer® no- additive Z plus tubes (Becton Dickinson 367624, Franklin Lakes, NJ). Serum lithium concentration was determined by means of an AVL 9180 electrolyte analyzer based on the ion- selective electrode (ISE) measurement principle (Roche Diagnostics 9115 Hague Road Indianapolis, IN 46256). The limit of detection (LOD) was 0.10 mEq/L and the limit of quantification (LOQ) 0.20 mEq/L. The between-day precision, expressed as coefficient of variation (CV) %, was 2.5 %, and the within-day precision was 3.4 %.

Samples with a lithium serum concentration <0.20 mEq/L were determined by means of a Perkin-Elmer AA200 flame atomic absorption spectrometer (Waltham, Massachusets, EEUU). The within day precision, the between day precision and the accuracy of the method was confirmed by the analysis of standard reference material Isetrol (Roce Diagnostics 26231). The CV for lithium between series was 1.6% and within series 2.4%. LOD was 0.004 mEq/L, and LOQ was 0.012 mEq/L.

2.4. Serum creatinine analysis

For creatinine analysis, maternal venous blood samples (5 ml) were collected into plastic BD Vacutainer® SSTTM tubes containing a silicone-separator gel (Becton Dickinson, 367986, Franklin Lakes, NJ). Serum creatinine concentration was determined by molecular absorption spectrometry using an Atellica CH analyzer (Chemistry System, Siemens Healthineers, Tarrytown, EEUU). LOD was 0.10 mg/dL, and LOQ was 0.15 mg/dL. Under the experimental conditions used, the coefficient of variation between series was ≤ 3.5%, and within series ≤ 4.0.

2.5. Statistical analysis

A descriptive analysis was conducted to characterize the sample using absolute and relative frequencies, means, standard deviations, or ranges, as appropriate. The lithium concentration/dose ratio (C/D) was calculated as an estimate of lithium clearance. This ratio was determined by dividing the serum lithium concentration (mEq/L) by the daily lithium dose (mg/day).

A linear mixed model was employed to analyse the longitudinal effects of pregnancy-related changes in GFR on litemias. Time points (i.e. preconception, pregnancy each trimester...) and lithium dose were included as fixed effects, while the individual mother was treated as random effect to account for repeated measurements. Additionally, in separate models, we considered parity status and daily lithium administration frequency as potential predictor variables. The average differences (95%CI) from baseline of litemias in each time point was estimated based on the model in order to study the dose adjusted changes of serum lithium concentrations along the perinatal period.

A second lineal mixed model was used to study the effect of pregnancy on renal function for those measurements where corresponding serum creatinine concentrations were obtained simultaneously with serum lithium concentrations. This model included serum creatinine concentrations as the response variable, time as a predictor, and the individual mother as random effect. Additionally, the model was used to estimate the average changes from baseline of serum creatinine concentrations at each time point. The same model was applied to analyse the evolution of the serum lithium concentration/lithium dose ration over time. For all models, restricted log-likelihood tests were performed to compare full models (including predictors) with null models (intercept

only), assessing the significance of the predictors. Furthermore, we also analysed the differences of serum creatinine concentrations between the last week before delivery and the first week after pregnancy by means of a linear mixed model.

Additionally, Pearson's correlation coefficient was calculated to assess the linear association between serum creatinine concentrations and both serum lithium concentrations and the lithium concentration/dose ratio. Lastly, we examined the association between renal dysfunction during pregnancy (defined as creatinine > 0.87 mg/dL, corresponding to 77 mmol/L, a dichotomous predictor variable) and serum lithium concentrations (response variable), specifically.

Data management and descriptive statistics were performed using SPSS for Windows (Version 25; IBM Corp., Armonk, NY, United States) and the R software package (V4.3.3; The R Foundation for Statistical Computing, Vienna, Austria). In particular, the R package lme4 was used to fit the linear mixed models (Bates, 2015). Statistical significance was determined using a two-sided p-value threshold of 0.05.

2.6. Ethics

This study was approved by the Ethics Committee for Drugs Research of the institution (HCB/2020/1305). Due that all data were retrospectively extracted from medical records, it was not necessary to obtain the written informed consent of each woman.

3. Results

3.1. Maternal characteristics

Table 1 shows maternal sociodemographic and psychiatric characteristics, obstetric outcomes and psychopharmacological treatment during the perinatal period. We identified 97 women in the clinical records that were eligible for study inclusion. Two women were excluded because analysis of serum lithium concentration measurements was performed in other laboratories. We included 95 women, most were Caucasian

(n=92, 96.8%), were married or had a partner (n=93, 97.9%) and around half (n=48, 50.5%) had university level education. The most common psychiatric diagnosis was a bipolar disorder type I (n = 84, 88.4%). There were 85 (89.5%) women with a single pregnancy, 6 (6.3%) women with two pregnancies, and 4 (4.2%) women with three pregnancies. In total, we have evaluated 109 pregnancies, of which 4 (3.7%) were twins.

Lithium carbonate (tablets of 400 mg of modified release of lithium carbonate) was used in all pregnancies, 51 (46.8%) of which completed a preconception psychiatric counselling visit at the PMHU between 1 and 2 years before the index pregnancy. According with their prescribing psychiatrist, women choose to continue lithium during the perinatal period in 73 (66.9%) pregnancies, to restart lithium in the second (n=20, 18.3%) or third trimester (n=6, 5.5%) after having been discontinued after confirmation of pregnancy in the first trimester, and to initiate in the third trimester to prevent postpartum relapse in 2 (1.8%) pregnancies. Other mood stabilizers with greater teratogenic risk were replaced by lithium preconceptionally (ac. valproic n=4,) or in the first trimester (ac valproic, n=3, ; carbamazepine n=1,). Forty-five pregnancies (41.3%) were on lithium monotherapy tthroughout the perinatal period.

The mean (SD) maternal age at time of conception was 34.6 (4.8) years. The mean (SD) gestational age at the first pregnancy visit was 11 (6.4) weeks. The rate of abortion was 10.1% (n=11). The most relevant obstetric complication was preeclampsia. The delivery was classified as a preterm birth (<37 weeks' gestation) in 11 (10.1%) pregnancies, and 52 (47.7%) had deliveries by caesarean section. See **Table 1.**

3.2. Course of serum lithium concentration in the perinatal period

We identified 1578 blood samples of which 318 samples met any of the exclusion criteria of our study. In total, 1260 serum lithium concentration measurements from 109 pregnancies were assessed. Preconception serum lithium concentrations measurements were available for 35 pregnancies (n=35, 32.1%) since most women were referred during the first (n=92, 78%) or second (n=20, 16.9%) trimester pregnancy. The mean (SD) number of samples per patient was 11.6 (6.2). **Figure 1** shows the distribution of serum lithium concentration measurements in the different time points periods.

Table 2 presents how lithium dosing strategies varied over time. Most lithium samples corresponded to multiple (≥2) daily dose (n=1160, 92.1%). The mean (SD) of lithium dose was decreased, relative to preconception levels [maintenance daily dose 1007 (290) mg/day] along pregnancy and in the first trimester of postpartum period and slightly increased in the second to fourth trimester of postpartum period.

Figure 2A represents the longitudinal pattern of serum lithium concentration measurements. According to the mixed-effects model for serum lithium concentrations, which included time and lithium dose as predictors, given a standardised daily lithium dose of 1000 mg, serum lithium concentrations decrease an estimate average of 30.2% (95%CI: 25.2,35.4) and 29.7% (95%CI:25.2, 34.0) in the first and second trimesters pregnancy. Following, according to the model-based prediction, the serum lithium concentrations increase in the third trimester of pregnancy but still remain below the levels during preconception (estimated reduction: 20.6% (95%CI:16.4, 23.7). In the first trimester postpartum concentrations increase with respect to preconception 2.4% (95%CI: -1.7, 7.1), in the second to fourth trimesters postpartum the relative increase is of 0.3% (95%CI:-4.6, 5.6)**;** see **Table 3A.** Other candidate predictors, including the frequency and parity did not significantly improve the performance of the model.

To accurately compare serum lithium concentrations, **Figure 2B** represents the longitudinal pattern of normalised serum lithium concentration to the total daily dose lithium (C/D ratio). According to the model for lithium C/D ratio, this ratio decreases an estimate average of 26.9% (95%CI: 21.4, 32.4) and 29.8% (95%CI:24.2, 35.2) in the first and second trimesters pregnancy, respectively, Following, according to the model-based prediction, the ratio increases but still remains below the levels during preconception (estimated reduction: 22.2%; 95%CI: 17.3, 26.9). In the first trimester postpartum, the ratio increases with respect to preconception 1% (95%CI: -3.5,6.2), and decreases 3.2% (95%CI: -9,2.0) in the second to fourth trimesters postpartum**. See Table 3B.**

3.3. Course of serum creatinine concentration and its correlation con serum lithium concentration along the perinatal period

We extracted serum creatinine concentration measurements to evaluate whether alterations in serum lithium concentrations were consistent with alterations in the glomerular filtration rate (GFR). In total, 1326 serum creatinine concentration

measurements were included. The distribution of serum creatinine concentration measurements was as follows: preconception (n=78, 5.9%), first trimester pregnancy (n=119, 9.0%), second trimester pregnancy (n=207, 15.6 %), third trimester pregnancy (n=480, 36.2%), first trimester postpartum (n=303, 22.8%) and second-fourth trimester postpartum (n=139, 10.5%).

Figure 2C represents the longitudinal pattern of serum creatinine concentration measurements. We obtain the following estimated mean serum creatinine concentrations according to the mixed effects model, which included period as only predictor: preconception, 0.73 mg/dL (95%CI: 0.70,0.76), first trimester pregnancy, 0.60 mg/dL (95%CI: 0.58, 0.63), second trimester pregnancy, 0.54 mg/dL (95%CI: 0.52, 0.57), third trimester pregnancy, 0.58 mg/dL (95%CI: 0.56, 0.60), first trimester postpartum, 0.68 mg/dL (95%CI: 0.66, 0.70), and second-four trimester pregnancy, 0.73 mg/dL (95%CI: 0.70, 0.75). The results of the model fit including the estimated relative changes are shown in **Table 3C.**

According to the model for serum creatinine concentrations, the creatinine measurements exhibited a similar longitudinal pattern as observed for serum lithium concentrations and lithium C/D ratios: serum creatinine concentrations decrease an estimate average of 17.9 % (95%CI:20.8, 14.0), 25.7% (95%CI:29.0, 22.2), and 20.5% (95%CI:23.5,18.1)i n the first, second and third trimester pregnancy , respectively , and 7.3% (95%CI: 9.9, 4.4) in the first trimester postpartum and 0.9% (95%CI: -4.4, 2.4) and the second-four trimester postpartum

We evaluated the correlation between paired serum creatinine concentration and serum lithium concentration along perinatal period (n=1174). Repeated measures correlations were statistically significant during pregnancy and postpartum with correlations ranging from 0.163 (first trimester postpartum) to 0.412 (third trimester pregnancy); see Supplementary Table x and **Figure 3.** See. Focusing on pregnancy, we found serum creatinine concentrations beyond the clinical threshold for renal dysfunction (>87mg/dL, corresponding to >77 µmol/L) in 3.1% of measurements (n=8). **Supplementary Material Figure 1.**

3.4. Serum lithium concentrations out of therapeutic range for maintenance treatment (≤ 0.40 mEq/L and ≥ 1.00 mEq/L) and their clinical implications.

A substantial proportion of serum lithium concentrations measurements along the perinatal period were ≤0.40 mEq/L (range 0.11 to 0.40 mEq/L) (n=268/1260, 21.3%), distributed as follows: preconception (n=9/87, 10.3%), first trimester pregnancy (n=52/130, 40%), second trimester pregnancy (n=79/220, 35.9%), third trimester pregnancy (n=1/432, 0.2%), first trimester postpartum (n=17/246, 6.9%) and second to fourth trimester postpartum (n=4/145, 2.8%). However, none of those litemias ≤0.4 mEq/L were associated with therapeutic failure. Ten (9.17%) pregnant women relapsed in the first trimester, 9 of the 26 pregnant women who choose to stop lithium when they found out about the pregnancy and one that discontinued lithium against medical advice.

On the other hand, the figures of litemias ≥1.00 mEq/L in the perinatal period were as follow: preconception (n=6/87, 6.9%), first trimester pregnancy (n=0/130, 0%), second trimester pregnancy (n=2/220, 0.9%), third trimester pregnancy (n=16/432, 3.7%), first trimester postpartum (n=16/246, 6.5%) and second to fourth trimester postpartum (n=11, 7.6%). Focusing on pregnancy, 14 cases (12.84%) had at least one serum lithium concentration measurement ≥1.0 mEq/L, of which 8 were isolated determinations. Eleven women relapsed in the postpartum period, five on them after stopped lithium by risk of preeclampsia.

4. Discussion

This observational retrospective study is the largest cohort who have quantified the longitudinal pattern of paired serum lithium and creatinine concentrations during the perinatal period in a naturalistic setting, as far as we know. We included 1326 serum creatinine concentration and 1260 serum lithium concentration measurements, of which 1174 were paired, in 109 pregnancies of 95 women. Compared with preconceptional baseline, serum lithium and creatinine concentration decreased in parallel during the first and second trimester of pregnancy, increased slightly in the third trimester remaining below the pre-pregnancy period. Throughout the postpartum period both gradually returned to their preconception level. Symptoms course worsened in some women who discontinued lithium treatment or with lithium below the therapeutic concentration of ≤ 0.40 mEq/L during pregnancy while during the postpartum some women decompensated

regardless of the lithium concentration. One third (5/14) of pregnant women who had at least a litemia >1.00 mEq/L presented obstetric complications.

Pregnancy causes a physiological and gradual increase in renal blood flow and glomerular filtration (GF) from the first trimester of pregnancy that produces an increase in lithium clearance and consequently a relevant decline in maternal serum lithium concentrations along pregnancy. The changes in serum lithium concentrations that we observed in our study are in line with previous studies although they have been carried out at different extraction time points (Clark et al., 2022; Schou et al., 1973; Westin et al., 2017; Wesseloo et al., 2017).

Individual variability in alteration in maternal serum lithium concentrations implies that serum lithium concentrations should be monitored even more closely during pregnancy and the postpartum period than in non-pregnant women. Serum lithium concentrations ≤0.40 mEq/L, concentrations that are considered subtherapeutic regardless of bipolar type and phase (Nolen WA et al., 2019), place the pregnant woman at risk of treatment failure and destabilization. In our study a high proportion serum lithium concentration measurement below <0.4 mEq/L were observed along pregnancy, being the highest proportion (40%) during the first and second trimester pregnancy. It is known that at the beginning of pregnancy women in general have worse adherence to any treatment. In all these cases, immediate dose increases were undertaken.

Particular attention is required for women presenting serum lithium concentration ≥ 1.00 mEq/L during pregnancy as in some cases it could be associated with kidney complications correlated with gestation (i.e. hypertension, preeclampsia) or with pre-existing kidney disease aggravated by pregnancy. (Deligiannidis et al, 2014; Newport et al., 2005). Based on serum creatinine reference ranges in females (0.51-1.02 mg/dL corresponding to 45-90 µmol/L), previously published in the literature (Wiles et al., 2019), a serum creatinine level greater than 0.87 mg/dL (77 µmol/L) should be considered outside the normal range for pregnancy and should raise suspicion of either undiagnosed chronic kidney disfunction (CKD) before conception or early development of acute kidney injury (AKI). The simultaneous analisys of serum lithium and serum creatinine concentrations during pregnancy can be helpful to discard serum lithium concentrations

alterations due to changes in renal function versus other factors (such as non-adherence, drug interaction, fluid intake, diet). which implicates that in this period clinicians need to be aware of the risk of lithium intoxication. We recommend re-check serum lithium concentrations after 3-5 days, investigate renal function (creatinine), consider a lithium dose decrease and clinical and analytical vigilance for lithium toxicity.

Creatinine clearance, a measurable surrogate marker of renal GF (Wiles et al., 2018) is a predictor of lithium elimination clearance. During uncomplicated pregnancy, serum creatinine falls to 0.40-0.60 mg/dL (35-55 µmol/L). This change reflects not only the pregnancy-induced increase in GFR, but also haemodilution deriving from approximately 30-50% plasma volume expansion necessary for the greater circulatory needs of the maternal organs. Based on serum creatinine reference ranges in females (0.51-1.02 mg/dL corresponding to 45-90 µmol/L), previously published in the literature (Wiles et al., 2019), a serum creatinine level greater than 0.87 mg/dL (corresponding to 77 µmol/L) should be considered outside the normal range for pregnancy and should raise suspicion of either undiagnosed chronic kidney disfunction (CKD) before conception or early development of acute kidney injury (AKI). In early postpartum, vascular volume rapidly decreases by approximately 40% and hyperfiltration has been shown to continue at levels of 20% above normal at postpartum week 2 and return to pre-pregnancy levels by 2-10 weeks postpartum (Odutayo and Hadunewich, 2012). As expected, in our study serum lithium and serum creatinine concentrations showed a highly similar longitudinal pattern throughout the pregnancy and postpartum (trimester). In our study, we observed that normalisation of renal function can take up to a few weeks after delivery as both mean lithium and creatinine blood levels were higher in the postpartum period than in the preconception period (+9% and +7% respectively). Preconception blood levels and corresponding preconception doses can be used as personalised reference values. Therefore, we recommend frequent monitoring (twice weekly) of lithium blood levels for the first 2 weeks postpartum. Relapse prevention prophylaxis in women with bipolar disorder with a higher lithium target level (for example $\geqslant$0.8 mmol/L) during the first month postpartum given the higk risk of relapse.

A multiple day dosing regime has been proposed to minimise foetal risk by minimising serum lithium concentrations (Horton et al. 2012). Many pregnant women do not follow treatment recommendations regarding dosage and duration of therapy, especially with medications prescribed for short-term use and pregnancy-related medications than with medications prescribed for chronic health conditions (De Korte et al., 2022). Clinically, intermittent adherence regarding dosage and duration of therapy, is the most common form of non-adherence and this means in the case of lithium that serum concentrations often fluctuate, and bipolar disorder prophylaxis may be suboptimal (Malhi, 2017). Enhancing lithium adherence among pregnant women is challenging and requires a multifaceted approach that involves psychoeducation and monitoring in the context of a therapeutic alliance (Berk, 2004, 2010a). It has been shown that patients who are informed about their illness and the importance of long-term treatment, have better compliance (Colom, 2003; Even, 2007). Other strategies that enhance adherence to treatment include educating the family and friends of the patients to recognise the early sings of relapse and institute suitable measures to curtail stressors (Rosa, 2007; Berk, 2011a). Further, encouraging patients to make a commitment to treatment prior to commencement (Rosa, 2007; Silverstone, 2000) and coupling pharmacotherapy with psychotherapy has been shown to greatly improve patients' outcomes (Colom, 2003; Even, 2007; Yatham, 2005).

The close monitoring of patients improves adherence in two ways. First, it allows tailoring of the therapeutic dose to suit the individual, so that therapeutic. Benefit is optimised and the likelihood of side effects is reduced (Silverstone, 2000). Second, regular monitoring increases clinical contact and therefore patients are likely to receive more frequent supervision and better education concerning their illness and its management (Rosa, 2007).

Strengths and limitations

We used a large sample size from a naturalistic setting. The study was conducted in a single university medical center, and we had access to clinical data such as the women's

psychopathological status, adherence to treatment or obstetric outcomes, and analytical data. Serum lithium and serum creatinine concentrations measurements were all analysed in the same laboratory, thereby contributing to reducing different management bias and laboratory results variations. Furthermore, for each women several measurements are included, adding to the value of the study and enabling the following of individual changes.

However, this study is not without limitations. This is an observational retrospective study, and this design could introduce some information bias. The cohort was attended on an outpatient basis and, as a result, a 12 ± 1 hour interval between lithium dose intake and measurement of serum lithium concentration may not always have been strictly maintained. Some overestimations of serum lithium concentration occurred in women who received their total daily dose of lithium once daily. Furthermore, not all women completed preconceptional counselling at our center with the objective of improving therapeutic compliance with lithium treatment during the perinatal period as well as receiving information on the identification of early signs of toxicity and adverse effect. Also not all women have preconception serum lithium concentrations in our laboratory as they were referred to our unit in first or second trimester pregnancy. Self-report based on interviews is generally acknowledged to result in underreporting of medication use during pregnancy. All these effects could have caused greater inter-variability of measured serum lithium concentrations.

5. Implications and Conclusions

Women with bipolar disorder of childbearing age who require lithium stabilization should be given the opportunity to weigh the risks and benefits of treatment during the perinatal period (preconception, pregnancy to 1 year postpartum) and develop an individualized treatment plan in a multidisciplinary specialised centre. Adecuate preconceptional counselling may attenuate some of the risk perception of lithium safety among pregnant women, improving adherence to treatment. Close clinical monitoring in combination with therapeutic drug monitoring (TDM) are needed for early detection of subtherapeutic or toxic serum lithium concentrations and for optimal lithium dosing to prevent bipolar disorder symptom recurrence while minimizing adverse effects in the mother. Following the results obtained in the study, we recommend to carefully monitor lithemia every 4 weeks until week 30 of pregnancy, then move to weekly lithemia until delivery and (bi-

)weekly during the first month postpartum. It is recommended that serum creatinine concentrations be assessed as a measure of monitoring lithium renal clearance. Many factors (compliance, diet, fluid intake, illness, drug interaction) can influence serum lithium concentrations and need to be considered when interpreting serum lithium concentrations. Particular attention is required for women presenting high serum lithium concentration (≥1.0 mEq/L) during pregnancy. We recommend re-check serum lithium concentrations after 3-5 days, investigate renal function (creatinine), and consider a lithium dose decrease and extra vigilance for lithium toxicity. Further large prospective studies are warranted to recommend a lithium dose regimem throughout the pregnancy and postpartum.

Authors Disclosure

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Author contributions

MLI: Conceptualization, Formal analysis, Investigation, Resources, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. MT: Resources, Validation, Writing – review & editing. KL: Formal analysis, Supervision, Visualization, Writing – review & editing. EP: Resources, Writing – review & editing. LGE: Resources, Writing – review & editing. EV: Conceptualization, Supervision, Writing – review & editing. RMS: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Table 1. Cohort characteristics: sociodemographic, obstetric outcomes and psychopharmacological treatment

Sociodemographic	Women (n=95) n (%) / mean (sd)
Ethnicity	
Caucasian	92 (96.8)
Othesr[a]	3 (3.2)
Educational level	
Primary	15 (15.8)
Secundary	32 (33.7)
University	48 (50.5)
Marital status	
Married or with partner	93 (97.9)
Single	2 (2.1)
Psychiatric diagnosis	
Bipolar disorder type I	84 (88.4)
Bipolar disorder type II	2 (2.1)
Bipolar disorder no otherwise	1 (1.1)
Cyclotimic disorder	1 (1.1)
Schizoaffective bipolar disorder	3 (3.2)
Recurrent major depressive disorder	4 (4.2)
Parity	
Primiparous	74 (77.9)
Multiparous	21 (22.1)
Medical risk factors[b]	
Yes	2 (1.83)
Obstetric outcomes	**Pregnancies (n =109)** n (%) / mean (sd)
Planned pregnancy at UPMH	50 (45.9)
Age at time of conception (years)	34.56 (4.76)
Gestational age at first visit (weeks)	11.01 (6.41)
Spontaneous pregnancy	97 (89.0)
Pregnancy complications	
Abortion	11 (10.1)
Spontaneous abortion 1st TM	10 (9.2)
Legally interrupted pregnancy[c]	1 (0.9)
Prematurity (< 37 wk)	11 (10.1)
Gestational diabetes	8 (7.3)
Polyhydramnios	9 (8.3)
Gestational hypertension	11 (10.1)
Preeclampsia	10 (9.2)
Early-onset preeclampsia (EOP)	4 (3.66)
Late-onset prreclampsia (LOP)	6 (5.50)
Type of delivery (n=97) [d]	
Vaginal	45 (46.3)
Cesarean section	52 (53.6)
Psychopharmacological treatment	**Pregnancies (n=109)** n (%) / mean (sd)
Lithium monotherapy	45
Lithium politherapy	64

Abbreviations: UPMH = Unit of Perinatal Mental Health; EOP= early onset preeclampsia; LOP=late onset preeclampsia

[a]Other ethnicity= 2 multiracial braziliam and 1 hispanic

[b]Medical risk factors: cardiovascular, central nervous system, gastrointestinal, hepatic, neuromuscular, renal, respiratory, thyroid

[c] One pregnancy was legally interrupted at gestational week 13 after a diagnosis of fetal hypoplastic left heart defect

Table 2. Lithium dosing scheme in the perinatal period

Time period[a]	Lithium					
	Blood measurements n (%)	Dose (mg/day) mean (sd)	Dose (mg/day) range	Lithium dosing scheme at each measurement daily dose n (%)		
				One	Two	Three
Preconceptional	87 (6.9)	1007 (290)	400-2000	10 (11,5)	66 (75.9)	11 (12.6)
Trimester 1	130 (10.3)	958 (353)	200-2000	16 (12.3)	86 (66.2)	28 (21.5)
Trimester 2	220 (17.5)	956 (291)	400-2000	11 (5)	153 (69.5)	56 (25.5)
Trimester 3	438 (34.3)	990 (285)	200-2000	34 (7,8)	287 (65.5)	117 (26.7)
Postpartum 1	246 (19.5)	987 (274)	400-1600	20 (8.1)	179 (72.8)	47 (19.1)
Postpartum 2-4	139 (11.5)	1050 (253)	600-1600	9 (6.5)	113 (81.3)	17 (12.2)

[a]Time periods: preconception (52 weeks preceding the estimated date of conception), first trimester pregnancy (0–13 weeks of gestation), second trimester pregnancy (14–26 weeks of gestation), third trimester pregnancy (27–40 weeks of gestation), first trimester postpartum (0-12 weeks postdelivery) and second to fourth trimester postpartum (13-52 weeks postdelivery).

Table 3. Linear mixed model analysis of serum lithium concentrations, serum lithium concentration/lithium dose ratio and serum creatinine concentrations.

3A. Estimated mean serum lithium concentrations at a given dose of 1000 mg [a]

	Serum lithium concentrations (mEq/L) mean (95% CI)	Change (%) mean (95% CI) [b]
Preconception	0.68 (0.64 to 0.72)	Reference
Trimester 1	0.48 (0.44 to 0.51)	-30.2 (-35.4 to -25.2)
Trimester 2	0.48 (0.45 to 0.51)	-29.7 (-34.0 to -25.2)
Trimester 3	0.54 (0.52 to 0.57)	-20.6 (-23.7 to -16.4)
Postpartum 1	0.70 (0.67 to 0.73)	2.4 (-1.7 to 7.1)
Postpartum 2-4	0.68 (0.65 to 0.72)	0.3 (-4.6 to 5-6)

[a]Linear mixed model analysis. Preconception is a reference category. Naive model: serum lithium concentration=intercept; final model: serum lithium concentration=intercept+dose+time (categorical). Restricted log likelihood ratio test: chi-squared = 631.7; df = 6; $p < 0.001$.

[b]Intervals for the % change are based on the 95% confidence intervals of the serum lithium concentrations

3B. Estimated mean serum lithium concentration /lithium dose (C/D) ratio during the perinatal period [a]

	Lithium C/D ratio [b] mean (95% CI)	Change (%) mean (95% CI) [c]
Preconception	0.73 (0.68 to 0.77)	Reference
Trimester 1	0.53 (0.49 to 0.57)	-26.9 (-32.4 to -21.4)
Trimester 2	0.51 (0.47 to 0.55)	-29.8 (-35.2 to -24.2)
Trimester 3	0.56 (0.53 to 0.60)	-22.2 (-26.9 to -17.3)
Postpartum 1	0.73 (0.70 to 0.77)	1.0 (-3.5 to 6.2)
Postpartum 2-4	0.70 (0.66 to 0.74)	-3.2 (-9.0 to 2.0)

Serum lithum concentration /lithium dose ratio (C/D ratio) was calculated as an estimation of lithium clearance during different time points in the perinatal period. The ratio was calculated as serum lithium concentration (mEq/L) divided by the lithium daily dose (mg(day) and multiplied by 1000.

[a]Linear mixed model analysis. Preconception is a reference category. Naive model: serum lithium concentration/lithium dose ratio=intercept; final model: serum lithium concentration/lithium dose ratio =intercept +time (categorical).

Restricted log likelihood ratio test: chi-squared = 291.5; df = 5; $p < 0.001$.

[c]Intervals for the % change are based on the 95% confidence intervals of the serum lithium concentration per lithium dose ratios

3C. Estimated mean serum creatinine concentrations (mg/dL) during the perinatal period

	Serum creatinine concentration (mg/dL) [a] mean (95% CI)	Change (%) [b] mean (95% CI)
Preconception	0.73 (0.70 to 0.76)	Reference
Trimester 1	0.60 (0.58 to 0.63)	-17.9 (-20.8 to -14.0)
Trimester 2	0.54 (0.52 to 0.57)	-25.7 (-29.0 to -22.2)
Trimester 3	0.58 (0.56 to 0.60)	-20.5 (-23.5 to -18.1)
Postpartum 1	0.68 (0.66 to 0.70)	-7.3 (-9.9 to -4.4)
Postpartum 2-4	0.73 (0.70 to 0.75)	-0.9 (-4.4 to 2.4)

[a]Linear mixed model analysis. Preconception is a reference category. Naive model: serum creatinine concentration=intercept; final model:serum creatinine concentration=intercept +time (categorical). Restricted log likelihood ratio test: chi-squared = 510.7; df = 5; $p < 0.001$.

[b]Intervals for the % change are based on the 95% confidence intervals of the serum creatinine concentrations

Table 4. Characteristics of women (n= 14) with lithemia ≥1.00 mEq/L along pregnancy and clinical implications

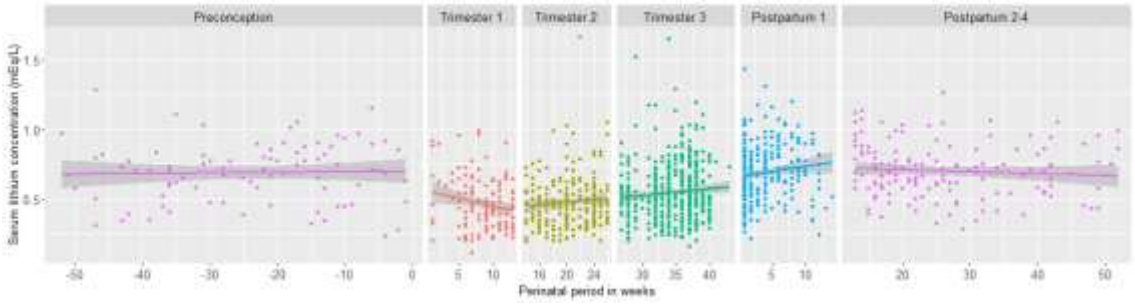
Case	Age (y)	Risk factors[a]	Parity	Pregnancy type	[Li]s >1.00 mEq/L					Diagnosis Treatment &Follow-up	Delivery GA (wk+d) & Type
					GA (wk+d)	[Li]s mEq/L	Li dose (mg/d)	[Cr]s mg/dL	Symptoms & Signs		
1	37	No	0	Single	34^{+0}	1.01	400-400-400	0.73	BP130/92 mmHg	Isolated diastolic blood pressure HTN at 4 months PP treated with AMLO 5 mg/d	34^{+4} , urgent C-section due to breech presentation
2	33	No	0	Single	38^{+6}	1.01	400-400-400	0.61	No	Isolated [Li]s ≥1.00 mEq/L	39^{+0}, vaginal
3	38	No	0	Single	32^{+5}	1.00	600-0-600	0.70	OGTT +	GDM treated with diet	
					34^{+4}	1.65	600-0-600	1.07	Hands mild tremor	Li dose gradual reduction	
					35^{+2}	1.29	200-0-400	1.05	Gly 114 Malleolar edema ++ BP145/95 mmHg Proteinuria 769	GDM treated with diet Mild preeclampsia Li dose reduction + QTP	
					36^{+0}	0.89	0	0.93	Gly 74 BP145/94 mmHg Proteinuria 622 AFI 28	GDM treated with diet + Mild Preeclampsia + Polyhydramnios Stop Li + QTP 800 mg/d	
					38^{+0}	0.32	0	1.20	Gly 74 BP152/112 mmHg Urine pr/cr ratio 2600	Severe preeclampsia Stop Li+ QTP 800 mg/d + LBT 100 mg/d + SO4Mg	38^{+0} , elective induction
4	40	Crohn' disease	0	Single	29^{+3}	1.02	400-0-600	0.59	No	Isolated [Li]s ≥ 1.00 mEq/L	
					34^{+4}	0.49	400-0-600	0.64	No	Stop Li 12 hours before C-section	34^{+4}, elective C-section due to fetal cardiac malformation
5	43	No	>1	Single	38^{+6}	1.03	800-400-400	0.83	No	Isolated [Li]s ≥ 1.00 mEq/L Li dose higher than ……	39^{+0}, elective C-section
6	32	No	0	Single	37^{+2}	1.03	800-0-400	0.57	No	Isolated [Li]s ≥ 1.00 mEg/L	38^{+1}, vaginal
7	36	No	>1	Single	38^{+0}	1.00	0-0-800	0.61	No	Isolated [Li]s ≥ 1.00 mEq/L	
					39^{+0}	1.10	0-0-800	0.79	No	Probable [Li] overestimation	39^{+6}, vaginal
8	38	No	0	Twin	20^{+1}	1.02	600-0-400	0.53	Transient increase in transaminases	Normal kidney function [Li]s re-check	
					26^{+0}	0.65	600-0-400	0.52	Gly	GDM treated with insulin	

					32^{+0}	1.17	600-0-400	0.78	Malleolar edema ++	Li dose gradual reduction [Li]s re-check	-
					36^{+4}	0.40	0	0.93	BP 140/90 mmHg Urine pr/cr ratio 2151	Mild pre-eclampsia	36^{+4} , elective C-section after fetal pulmonar maturation
9	32	No	0	Single	35^{+4}	1.13	400-0-600	0.61	No	Isolated [Li]s $\geq$ 1.00 mEq/L	
					38^{+1}	0.81	400-0-400	0.67	No	Normal kidney function	38^{+1} . urgent C-section due to loss of fetal well-being
10	38	No	0	Single	35^{+6}	1.29	400-400-400	0.46	No	Isolated [Li]s $\geq$ 1.00 mEq/L	
					40^{+3}	0.51	1000-0-0	0.56	No	Normal kidney function	40^{+3} , elective induction due to uterine atony
11	39	No	>1	Twin	31^{+0}	1.66	800-0-800	0.69	Nausea, vomiting, tremor and fatigue	Mild Li intoxication Li dose gradual reduction	
					32^{+1}	2.60	800-0-600	0.74	Tachycardia, hypertonia, confusion, agitation, delirium	Moderate Li intoxication Li suppression, hyperhidratation	
					33^{+2}	0.34	0	0.88	BP 140/90 mmHg Proteinuria 786 Urine pr/cr ratio 1222	Mild pre-eclampsia	33^{+2} , elective C-section
12	45	No	0	Single	38^{+6}	1.19	200-200.400	0.59	BP 138/78 mmHg Urine pr/cr ratio 197	Suspect preeclampsia Li dose reduction	
					39^{+2}	0.63	0-0-400	0.68			39^{+2} , elective induction due to maternal age and macrosomia
13	45	No	0	Single	30^{+5}	1.52	1200-0-800	0.46	BP 140/92 mmHg	HTN Li dose reduction	
					33^{+5}	0.99	600-0-400	0.54	BP142/92 mmHg Proteinuria 435 Urine pr/cr ratio 407	Mild pre-eclampsia Li dose reduction	
					37^{+1}	1.41	0-0-400	0.61	BP152/92 mmHg Urine pr/cr ratio 529	Mild pre-eclampsia Li dose reduction	37^{+1}, elective C-section
14	47	No	0	Single	26^{+4}	1.05	400-400-400	0.71	No	Isolated [Li]s $\geq$ 1.00 mEq/L [Li]s re-check	-
					39^{+1}	0.68	400-400-400	0.88	No		39^{+1} , elective C-section

due to maternal age

Abbreviations: AFI=amniotic fluid index; AMLO=amlodipine; SO4Mg= magnesium sulfate; wk=week; d=day; BP=blood pressure (mmHg) ; GA=gestational age ; LBT= labetalol; Li=lithium; QTP=quetiapine; SO4Mg= magnesium sulphate; Cr=creatinine; OGTT=oral glucose tolerance test; EOP= early onset preeclampsia ; GHTN=gestational hypertension; C-section= cesarea section; Urine pr/cr ratio=urine protein/creatinine ratio (mg/g)
[a]Risk factors:

A



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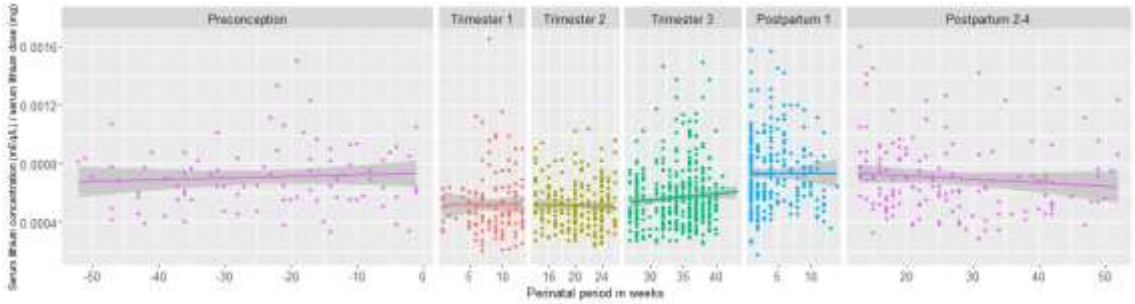
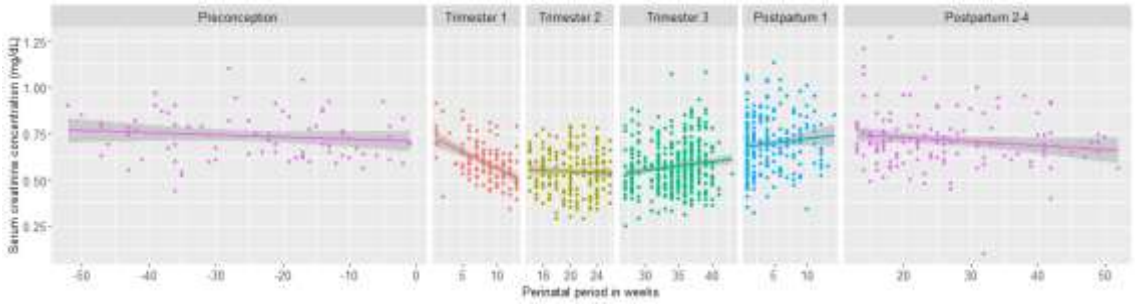
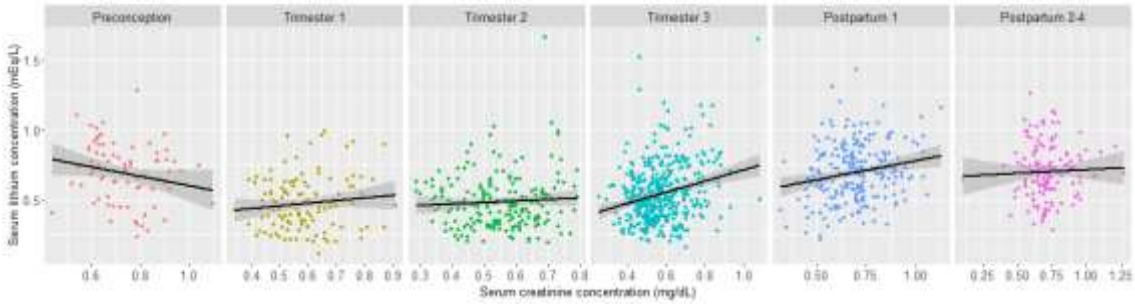


C



Abbreviations: Preconception: 52 weeks preceding the estimated date of conception; Trimester 1 pregnancy: 0–13 weeks of gestation; Trimester 2 pregnancy: 14–26 weeks of gestation; Trimester 3 pregnancy: 27–40 weeks of gestation; Postpartum 1: 0-12 weeks postdelivery; Postpartum 2-4: 13-52 weeks postdelivery.

Figure 2. Course of serum lithium concentration, serum lithium concentration/dose ratio and serum creatinine concentration during the perinatal period. Figure (2A) shows the measured unadjusted serum lithium concentrations for all mothers. Figure (2B) shows the same observations after being adjusted for lithium dose. The commonly reference serum concentration range for lithium is 0.5-1.0 mEq/L. Figure (2C) shows the measured serum creatinine concentrations. The upper limits of normal serum creatinine concentration are: non-pregnant women (1.02 mg/dL) and for pregnancy in sequential trimesters (0.86 mg/dl in the 1st trimester, 0.81 mg/dl in the 2nd and 0.87 mg/dl in the 3rd trimester).



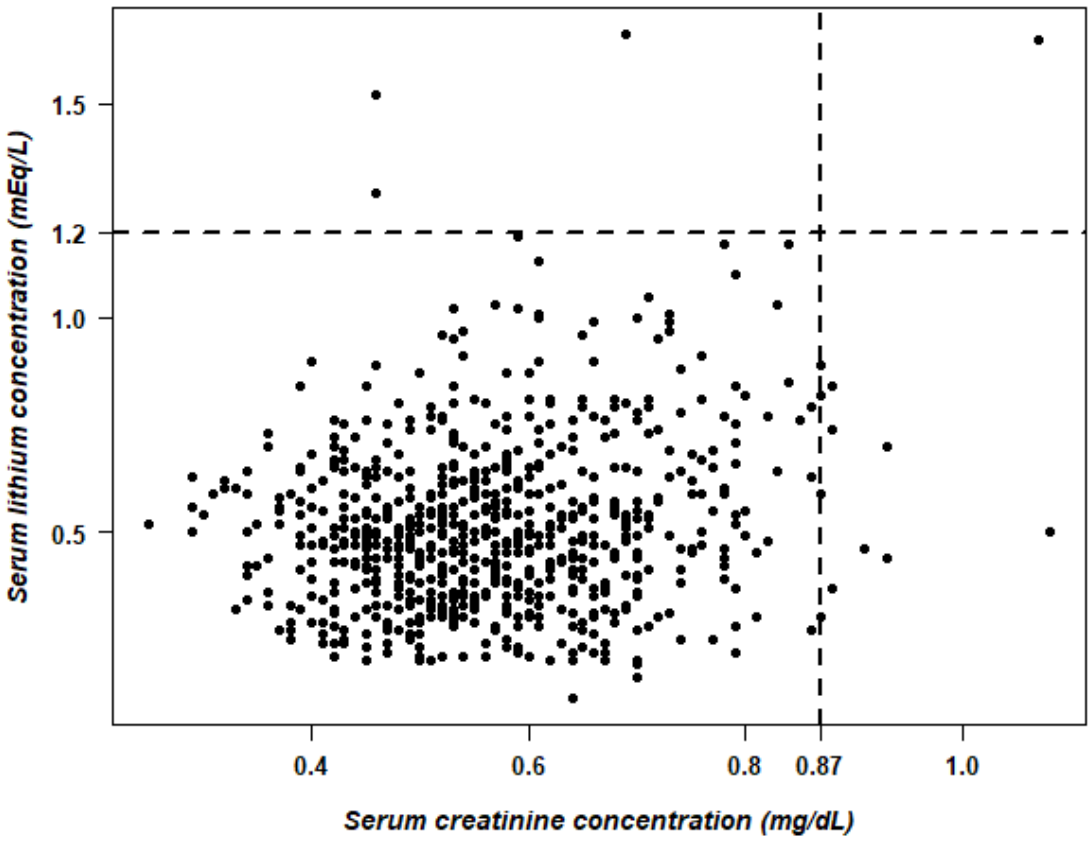
Abbreviations: Preconception: 52 weeks preceding the estimated date of conception; Trimester 1 pregnancy: 0–13 weeks of gestation; Trimester 2 pregnancy: 14–26 weeks of gestation; Trimester 3 pregnancy: 27–40 weeks of gestation; Postpartum 1: 0-12 weeks postdelivery; Postpartum 2-4: 13-52 weeks postdelivery.

Figure 3. Joint distribution of serum lithium (mEq/L) and serum creatinine (mg/dL) concentrations during the perinatal period.

Supplementary Table 1. Repeated measures correlation between serum lithium concentration and serum creatinine concentration.

	n	r	95% CI		p-value
			Low	Up	
Period[a]					
Preconception	78	-0.074	-0.354	0.217	0.619
Trimester 1	119	0.393	0.15	0.591	0.002
Trimester 2	205	0.182	0.01	0.344	0.039
Trimester 3	403	0.412	0.316	0.5	<0.001
Postpartum 1	230	0.163	0.002	0.316	0.047
Postpartum 2-4	139	0.316	0.112	0.493	0.003

[a]Preconception: 52 weeks preceding the estimated date of conception; Trimester 1 pregnancy: 0–13 weeks of gestation; Trimester 2 pregnancy: 14–26 weeks of gestation; Trimester 3 pregnancy: 27–40 weeks of gestation; Postpartum 1: 0-12 weeks postdelivery; Postpartum 2-4: 13-52 weeks postdelivery.



Supplementary Figure 1. Joint distribution of serum lithium concentration[a] (mEq/L) and serum creatinine concentration[b] (mg/dL) during pregnancy (n=727). [a] Dotted line indicate upper threshold for serum lithium concentration. [b] Dotted line indicate upper threshold for serum creatinine concentration during pregnancy. Based on serum creatinine reference ranges in females (0.51-1.02 mg/dL corresponding to 45-90 µmol/L), previously published in the literature (Wiles et al., 2019), a serum creatinine level greater than 0.87 mg/dL (77 µmol/L) should be considered outside the normal range for pregnancy and should raise suspicion of either undiagnosed chronic kidney disfunction (CKD) before conception or early development of acute kidney injury (AKI).

8.2 Artículo 2: resumen estructurado

Imaz ML, Torra M, Langohr K, Arca G, Soy D, Hernández AS, García-Esteve L, Vieta E, Martin-Santos R. Peripartum lithium management: Early maternal and neonatal outcomes. J Affect Disord. 2024; 366:326-334.

FI:4,9 Cuartil: Q1 Categoría: Psiquiatría

Introducción: Se ha sugerido que una reducción de la dosis de litio del 30 al 50 % o la interrupción del litio 24 a 48 h antes del parto podrían minimizar las complicaciones neonatales. Investigamos los cambios en la litemia materna durante el parto después de una breve interrupción, la transferencia placentaria de litio en el momento del parto y la asociación entre la litemia neonatal en el momento del parto y los resultados neonatales agudos.

Método: Se realizó un estudio de cohorte observacional retrospectivo en un hospital universitario (noviembre/2006-diciembre/2018). Los datos se extrajeron de las historias clínicas. Se incluyeron mujeres psicopatológicamente estables, con embarazo único, tratadas con litio al final del embarazo, con al menos una litemia materna y neonatal al momento del parto. El litio se suspendió 12 horas antes de una cesárea o inducción programada, o el día del ingreso al hospital; y reiniciado 6-12 h posparto.

Resultados: Se incluyeron 66 pares madre-hijo y se obtuvieron 226 litemias maternas y 66 neonatales. Se encontraron ligeras fluctuaciones de la litemia materna cercanas a 0,20 mEq/L y una recaída posparto temprana del 6 %. La relación media (DE) de litemia intraparto del cordón umbilical/madre fue de 1,10 (0,17). Cincuenta y seis por ciento de los neonatos presentaron complicaciones agudas transitorias. La hipotonía neonatal fue el resultado más frecuente (N = 15). La litemia media fue 0,178 mEq/L mayor en aquellos con hipotonía que en aquellos sin ella (p = 0,028).

Limitaciones: Es una cohorte retrospectiva de un tamaño de muestra moderado de embarazos sanos sin complicaciones y los resultados no se pueden generalizar a todas las embarazadas tratadas con litio.

Conclusiones: El litio se transfiere completamente a través de la placenta. Una breve interrupción del litio antes del parto se asoció con ligeras fluctuaciones de la litemia materna. Los recién nacidos expuestos intraútero al litio presentan efectos agudos frecuentes pero transitorios.

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Research paper

Peripartum lithium management: Early maternal and neonatal outcomes

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ABSTRACT

Background: It has been suggested that a 30–50 % lithium dose reduction or lithium discontinuation 24-48 h before delivery could minimize neonatal complications. We investigated the maternal lithemia changes around delivery after a brief discontinuation, the placental transfer of lithium at delivery, and the association between neonatal lithemia at delivery and acute neonatal outcomes.
Methods: A retrospective observational cohort study was conducted in a teaching hospital (November/2006-December/2018). Data was extracted from the medical records. We included psychopathologically stable women, with a singleton pregnancy, treated with lithium in late pregnancy, with at least one maternal and neonatal lithemia at delivery. Lithium was discontinued 12 h before a scheduled caesarean section or induction, or at admission day to hospital birth; and restarted 6-12 h post.
Results: Sixty-six mother-infant pairs were included, and 226 maternal and 66 neonatal lithemias were obtained. We found slight maternal lithemia fluctuations close to 0.20 mEq/L, and early postpartum relapse of 6 %. The mean (SD) umbilical cord/mother intrapartum lithemia ratio was 1.10 (0.17). Fifty-six percent of neonates presented transient acute complications. Neonatal hypotonia was the most frequent outcome ($N = 15$). Mean lithemia were 0.178 mEq/L higher in those with hypotonia than in those without ($p = 0.028$).
Limitations: It is a retrospective cohort of a moderate sample size of healthy uncomplicated pregnancies and results cannot be generalized to all pregnant treated with lithium.
Conclusions: Lithium transfers completely across the placenta. A brief predelivery lithium discontinuation was associated with slight maternal lithemia fluctuations. Neonates exposed intrautero to lithium present frequent but transient acute effects.

1. Introduction

The perinatal period is a time of increased vulnerability for women with affective and non-affective psychotic disorders (Di Florio et al., 2013; Taylor et al., 2020b). Especially, women with severe bipolar disorder or untreated bipolar disorder and those with non-affective psychotic disorder are at high risk of relapse in the postpartum period that during pregnancy (Sharma et al., 2020; Viguera et al., 2011; Wesseloo et al., 2016). Lithium remains the gold standard treatment for preventing recurrences in bipolar disorder type I (with mania and eventually major depression), and II (with depression and hypomania) (Tondo et al., 2019). It also has evidence of effectiveness of lithium augmentation in the treatment of refractory depression and in the treatment of affective symptoms in schizoaffective disorder (Leucht et al., 2015; Taylor et al., 2020a). During the perinatal period lithium is proven effective as maintenance therapy for bipolar disorder and to

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prevent postpartum psychosis (Bergink et al., 2012; Wesseloo et al., 2016). Although one of the main concerns around the use of lithium during pregnancy is teratogenicity, the risk-benefit balance has lately shifted toward maintaining lithium during pregnancy to avoid the consequences of relapse in the mother (Bergink, 2023).

Lithium is a monovalent cation that is absorbed rapidly through the upper gastrointestinal tract and is almost exclusively renal eliminated without undergoing metabolization. Serum lithium concentrations mainly depend on intravascular volume and glomerular filtration rate (GFR). Lithium clearance is usually 20 % to 30 % of the GFR and thus varies with it (Grandjean and Aubry, 2009; Thomsen and Schou, 1999).

Pregnancy affects all aspects of kidney physiology altering the pharmacokinetics of lithium, which may affect both its efficacy and safety. Glomerular filtration rate increases early during pregnancy at one month after conception, peaks at approximately 40–50 % above pre-pregnancy levels by the early second trimester and declines slightly toward term (Cheung and Lafayette, 2013). Lithium elimination clearance parallels changes in GFR (Clark et al., 2022) and this result in reduced maternal serum lithium concentrations across pregnancy (Clark et al., 2022; Schou et al., 1973; Westin et al., 2017; Wesseloo et al., 2017). A retrospective study of perinatal lithium pharmacokinetics has found that serum lithium concentrations increase slightly in the third trimester but remained 21 % below the pre-pregnancy baseline (Wesseloo et al., 2017). Moreover, natrium depletion, dehydration, diet, drug interactions, obstetrical complications (e.g. pre-eclampsia) and inconsistent treatment adherence can all cause changes in maternal serum lithium concentration (Clark et al., 2022). In order to maintain serum lithium concentration within the therapeutic optimal level of 0.5–0.8 mEq/L, lithium doses generally need to be adjusted during pregnancy (Westin et al., 2017).

Lithium equilibrates completely across the placenta (Newport et al., 2005). Higher maternal serum lithium concentrations at delivery have been associated with varied neonatal complications (hypoglycaemia, cardiac dysfunction, diabetes insipidus, thyroid dysfunction, respiratory distress, hypotonia and lethargy) requiring neonatal supportive care (Kozma, 2005; Newport et al., 2005; Pinelli et al., 2002). A previous retrospective observational cohort study did not observe a significant association between neonatal serum lithium concentrations at delivery and neonatal outcomes (Molenaar et al., 2021). A recent retrospective observational cohort study of neonates born to women with bipolar disorders treated with different psychopharmacs, with or without lithium, found that exposure to lithium was not associated with greater risk of neonatal ward admission (Schonewille et al., 2023). Moreover, having a bipolar disorder or schizophrenia, has been associated to slightly increased risk of obstetric and neonatal complications independent of medication used during pregnancy (Bennedsen et al., 1999; Bodén et al., 2012; Schonewille et al., 2023).

In early postpartum, vascular volume rapidly decreases by approximately 40 % and renal lithium clearance decreases to pre-pregnancy levels (Grandjean and Aubry, 2009). Hyperfiltration has been shown to continue at levels of 20 % above normal at postpartum week 2 and resolve by 1 month postpartum (Odutayo and Hladunewich, 2012; Wesseloo et al., 2017). Lithium has a narrow therapeutic range (0.5–1.2 mEq/L), and in consequence, increased serum lithium concentrations (>1.5 mEq/L) may manifest as adverse effects in the mother (Hiemke et al., 2018), especially when an increased dose used during pregnancy is continued into the postpartum (Blake et al., 2008; Deligiannidis et al., 2014). If lithium is discontinued during pregnancy, it should be restarted immediately after delivery. During the first month postpartum a high target therapeutic serum lithium concentration (e.g. 0.8–1.0 mEq/L) has been recommended to optimize maternal relapse prevention (Wesseloo et al., 2016; Wesseloo et al., 2017).

Adequate monitoring of pregnant women treated with lithium around delivery is needed for early detection of subtherapeutic or toxic serum lithium concentrations to minimize potential mother and fetal/neonatal adverse effects. In the current research we want to study the behaviour of lithium around delivery in a large and homogeneous cohort of mothers treated with lithium in late pregnancy and their neonates. We evaluated the maternal serum lithium concentration changes around delivery, the lithium trans placental passage, and the association between neonatal serum lithium concentrations at delivery and acute neonatal outcomes.

2. Methods

2.1. Participants

Women attended in a perinatal psychiatric outpatient clinic of a single tertiary university hospital (November 2006–December 2018), and treated with lithium in the perinatal period, were evaluated for eligibility to participate in this retrospective observational cohort study. Only psychopathologically stable women with healthy uncomplicated singleton pregnancy who used lithium in late pregnancy, and with at least one serum lithium concentration measurement obtained both in mother (vein puncture the admission day to hospital birth or at delivery) and in neonate (umbilical cord or neonatal vein puncture 24 h post-delivery) were included in this cohort. Stable treated hypothyroidism was not an exclusion criteria.

2.2. Data collection and procedures

Study included demographic, psychiatric, obstetric, and early neonatal data for each woman and her corresponding pregnancies obtained from the hospital medical records. Obstetric complications evaluated included gestational diabetes, gestational hypertension, pre-eclampsia, polyhydramnios, oligohydramnios and premature rupture of membranes. Neonatal outcomes evaluated included prematurity (delivery prior to 37 weeks gestational age), birth weight, Apgar score at 1 and 5 min, umbilical cord arterial pH (UApH) and base excess (BE) values, serum TSH value, acute complications after a completed physical examination of the newborn (e.g. respiratory, circulatory, neurological, and other body systems), neonatal intensive (NICU, level IV) and intermediate (NICU, level II) care unit admission, and hospitalization duration after birth. We extracted information of all reported prenatal and postnatal congenital malformations. Positive neonatal findings were validated with a second expert neonatologist.

In line with the current NICE guideline (NICE CG192, 2014), the standard of care of the Perinatal Mental Health Unit Clinic-BCN is to monitor serum lithium concentrations every four-weeks until 34 weeks of pregnancy and then at least once weekly until delivery. Our recommendation for the management of lithium in the peripartum included: 1) the advise to suspend lithium administration 12 h before a scheduled caesarean section or induction or at admission day to hospital birth in the case of spontaneous deliveries, 2) the recommendation to restart lithium treatment 6 h after vaginal delivery, or 12 h post-delivery in case of caesarean birth; 3) to obtain serum lithium concentrations measurements simultaneously in mother-neonate pair at delivery; 4) to obtain mother serum lithium concentration measurement at day 2 ± 1 postpartum, followed by (bi-) weekly during the first month postpartum. At the prenatal visit (week 33–35 of gestation), the psychiatrist carries out with each woman the risk-benefit analysis of maintaining the lowest effective lithium dose, or interrupting lithium dose around delivery. Each woman was given a written delivery planning kit containing the lithium extraction instructions and the tubes to perform the maternal (venous blood) and neonatal (umbilical cord) lithium measurements at delivery.

The maternal lithium therapeutic drug-monitoring (TDM) database contained information about the prescribed lithium dose and the dosing frequency, time of last lithium intake, time of blood sampling, serum lithium concentrations and types and doses of concomitant drugs. The peripartum time course of serum lithium concentration measurement was synchronized based upon the date of delivery (D0). Different time

points of extraction before and after delivery were: most recent pre-partum visit under steady-state condition (D-3), day before hospital birth (D-2), admission day to hospital birth (D-1), postpartum day 1 to day 7 (D+1 to D+7) and most recent post-partum visit under steady-state condition (D+8). The neonatal TDM databases contained serum lithium concentration in umbilical cord or first day of life.

2.3. Serum lithium analysis

For lithium analysis, maternal venous blood (5 mL), umbilical cord blood (5 ml) and neonates venous blood (2 mL) samples, were collected into BD Vacutainer® no- additive Z plus tubes (BD Diagnostics, Pre-analytical Systems, Franklin Lakes, NJ 07417). Lithium concentrations were determined by means of an AVL 9180 electrolyte analyser based on the ion- selective electrode (ISE) measurement principle (Roche Diagnostics 9115 Hague Road Indianapolis, IN 46256). Lithium concentrations were reported in mEq/L, with two significant digits after the decimal points. A 2-point calibration were performed every 4 h with a measurement range between 0.10 and 6.00 mEq/L. Limit of quantification (LoQ) was 0.20 mEq/L and detection limit (LoD) was 0.10 mEq/L. The within-day precision, expressed as coefficient of variation (CV) %, was between 0.97 and 4.1 %, and the between-day precision ranged between 1.3 and 6.4 %.

2.4. Statistical analysis

A descriptive analysis was performed to characterize the sample and the placental passage of lithium using, either absolute, and relative frequencies or means, standard deviations, and ranges as appropriate. The differences of maternal characteristics of mothers with monotherapy and those with polytherapy were quantified with the effect size measures Cohen's d (numeric variables) or Cohen's h (categoric variables). According to Cohen, values of both *d* and *h* equal to 0.2, 0.5, and 0.8 may be considered small, medium, and large (Cohen, 1988). To study the course of maternal serum lithium concentrations after a briefly discontinuation of lithium treatment around delivery, mean absolute and relative changes together with the corresponding 95 % confidence intervals for paired data were computed. This was done on the one hand, for the changes from both the day before hospital birth and the admission day to hospital birth and, on the other hand, for the changes from delivery until postpartum days 2, 3, and 7, respectively. The ratio of serum lithium concentration in umbilical cord to that in maternal serum was calculated for each maternal-infant pair as index of lithium placental passage. In addition, the relation between umbilical cord and maternal serum lithium concentrations surrounding delivery was illustrated with a scatterplot and quantified by means of Pearson's correlation coefficient.

The relation between neonatal serum lithium concentrations and neonatal outcomes was analysed using *t*-tests. Specifically, t-tests were conducted to compare the means (SD) of serum lithium concentrations between neonates with and without complications. This analysis was performed only if there were >10 cases of complications in the sample to avoid unreliable statistical conclusions due to small sample size.

All data were analysed using SPSS for Windows (Version 25; IBM Corp., Armonk, NY, United States) and the R software package (V4.3.3; The R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at 0.05 two sided.

2.5. Ethics

The Ethics Committee for Drugs Research of the Hospital Clinic (HCB/2020/1305) approved the study. Written informed consent was not obtained due the retrospective extraction from medical records.

3. Results

3.1. Maternal characteristics

Table 1 shows mother characteristics. We identified data from 97 women and 111 pregnancies that were eligible for study inclusion. Forty-five pregnancies were excluded because there where first trimester abortions ($N = 13$), twin pregnancy ($N = 4$), serum lithium concentrations measurements were not available at delivery ($N = 27$) and the analysis was performed at another laboratory ($N = 1$). In total, we included 60 women and six women contributed with 2 pregnancies each. Each pregnancy was counted separately (66 mother-infant pairs). The most common psychiatric diagnosis was a bipolar disorder type I ($N = 54$, 90 %). The remaining women ($N = 6$, 10 %) were diagnosed with bipolar disorder type II ($N = 1$, 1.6 %), bipolar disorder nos ($N = 1$, 1.6 %), cyclothymic disorder ($N = 1$, 1.6 %), schizoaffective bipolar disorder ($N = 1$, 1.6 %) or recurrent depressive disorder ($N = 2$, 3.3 %). See also Supplementary Fig. 1, a flow chart of the study.

Mean (SD) maternal age at time of conception was 33.79 (5.05) years. All women received psychiatric prenatal care for the majority of pregnancy. Fourteen women were treated with levothyroxine for hypothyroidism and were stable. The duration of the pregnancy was between −29 days and + 9 days with respect to the estimated due date. The mean (SD) time from admission day to hospital birth (D-1) to delivery (D0) was 16.37 (11.74) h. Thirty-four (51.50 %) of the deliveries were by caesarean section, 18 (27.30 %) were schedule caesarean section, and 16 (24.20 %) urgent caesarean section for failed induction of labour, respectively.

All patients were treated with lithium carbonate (tablets of 400 mg of modified release of lithium carbonate, Plenur®). Most women ($N = 56$, 85 %) used lithium multiple daily dosing, and 15 % of women ($N = 10$) once-daily dose. Forty mothers (61 %) were on lithium monotherapy at the time of delivery. Polytherapy combinations ($N = 26$, 39 %) included lithium and antipsychotic [quetiapine ($N = 14$), olanzapine ($N = 4$), haloperidol ($N = 1$), paliperidone ($N = 1$), aripiprazole ($N = 1$)], lithium combined with two antipsychotics [quetiapine plus aripipiprazole ($N = 1$)], lithium and antidepressant [fluoxetine ($N = 4$), paroxetine ($N = 1$), venlafaxine ($N = 1$), imipramine ($N = 1$)] or lithium and antipsychotic combined with an antidepressant [quetiapine plus fluoxetine ($N = 1$)]. None were taking other medication known to interact with lithium (e.g. diuretics or non-steroidal anti-inflammatories).

Concerning maternal characteristics, differences between mothers with lithium poly- and monotherapy with respect to age (Cohen's d = 0.19), ethnicity (Cohen's h = 0.08), marital status (h = 0.39), education level (h = 0.18), and number of prior pregnancies (d = 0.10) could be considered of small or medium size, whereas a larger difference was observed for tobacco use (h = 0.46).

3.2. Characteristics and course of maternal serum lithium concentration around delivery

Table 2 shows the characteristics and course of maternal serum lithium concentration at different extraction time points (D-3 to D+8). The maternal lithium TDM database around delivery (from D-2 to D+7) consisted of 226 serum lithium concentration measurements and the distribution were as follow: 26 (11.50 %) at D-2, 23 (10.17 %) at D-1, 64 (28.31 %) at D0, 112 (49.56 %) in the week after D0 [15 (13.39 %) D+1, 35 (31.25 %) D+2, 19 (16.96 %) D+3, 13 (11.60 %) D+4, 5 (4.46 %) D+5, 5 (4.46 %) D+6, and 21 (17.85 %) at D+7]. See Supplementary Fig. 1.

In the whole sample ($N = 66$), at extraction time point D-3, 5.59 (8.94) days before delivery, the mean (SD) lithium dose was 993.94 (284.9) mg/day, and the mean (SD) serum lithium concentration was 0.58 (0.21) mEq/L. A considerable proportion of serum lithium measurements (28/66, 42.40 %) were at subtherapeutic threshold for effective mood stabilisation (<0.5 mEq/L). However, all women were

Table 1
Maternal and neonatal characteristics and serum lithium serum concentrations around delivery.

Lithium therapy						
	All cases	Monotherapy	Polytherapy			
			All	Li + AP	Li + AD	Li + AP + AD
	N = 66	N = 40	N = 26	N = 19	N = 6	N = 1
Maternal characteristics Mean/SD/N (%)						
Age at time of delivery	34.80 (5.02)	34.40 (5.11)	35.35 (4.93)	36 (5.16)	33.50 (4.41)	34
Caucasian	64 (97.00)	39 (97.50)	25 (96.20)	18 (94.70)	6 (100)	1
University degree	32 (48.50)	18 (45.00)	14 (53.80)	10 (52.60)	3 (50.0)	1
Married or living together	65 (98.50)	40 (100)	25 (96.20)	18 (94.70)	6 (100)	1
Smoking in late pregnancy	15 (22.7)	6 (15.00)	9 (34.60)	8 (42.10)	1 (16.70)	0
Primiparous	49 (74.20)	29 (72.50)	20 (76.90)	15 (78.90)	4 (66.70)	1
Caesarean_section	34 (51.50)	15 (37.50)	19 (73.10)	16 (84.20)	3 (50.00)	0
Meconium in amniotic fluid	6 (9.10)	6 (15.00)	0	0	0	0
Prolonged rupture of membranes[a]	11 (16.70)	6 (15.00)	5 (19.20)	3 (15.80)	2 (33.30)	0
Lithium dosage closest to delivery	993.94 (284.94)	935.00 (257.75)	1084.62 (305.53)	1136.84 (326.96)	966.67 (196.63)	800
Neonatal characteristics Mean/SD/N (%)						
Preterm birth (<37 weeks)	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Macrosomia (>4000 g)	10 (15.20)	7 (17.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Apgar score$_{1\ min}$ < 6	3 (4.50)	3 (7.50)	0	0	0	0
Apgar score$_{5\ min}$ < 8	0	0	0	0	0	0
pH UC arterial	7.22 (0.07)	7.21 (0.08)	7.23 (0.07)	7.24 (0.06)	7.18 (0.07)	–
BE UC arterial (mmol/L)	−7.48 (2.62)	−7.76 (2.46)	−6.99 (2.88)	−6.56 (2.50)	−8.37 (3.98)	–
Acute complications[b]:						
Hypotonia	15 (22.72)	10 (25.00)	5 (19.23)	2 (10.50)	3 (50.00)	0
Hypertonía	4 (6.10)	2 (5.00)	2 (7.70)	1 (10.50)	0	0
Tremors	8 (12.10)	3 (7.50)	5 (19.20)	4 (21.10)	1 (16.70)	0
Sucking difficulties	4 (6.00)	3 (7.50)	1 (3.85)	1 (5.26)	0	0
Systolic murmur	8 (12.10)	5 (12.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Respiratory distress[c]	3 (4.50)	3 (7.50)	0	0	0	0
Cyanosis	1 (1.50)	1 (2.50)	0	0	0	0
Hepatomegaly	1 (1.50)	1 (2.50)	0	0	0	0
Hyperbilirubinemia	6 (9.10)	3 (7.50)	3 (11.50)	3 (15.80)	0	0
Hypoglycemia	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Skin lesions[d]	3 (4.50)	2 (5.00)	1 (3.85)	0	1 (16.70)	0
Cefalhematoma	3 (4.50)	2 (5.00)	0	0	1 (16.70)	0
TSH serum (mUI/L)	5.04 (3.48)	4.97 (3.33)	5.19 (3.78)	5.45 (3.70)	4.94 (4.39)	1.63
Hospital stay (days) (N = 65)	3.17 (1.21)	3.05 (1.20)	3.38 (1.27)	3.44 (1.42)	3.33 (0.81)	2

Abbreviations: BE = base excess; Li = lithium; Li + AP = lithium + antipsychotic; Li + AD = lithium + antidepressant; Li + AP + AD = lithium + antipsychotic + antidepressant; TSH = tyroid stimulating hormone.

[a] Prolonged rupture of membranes (>24 h): preterm (N = 1), term (N = 10).

[b] After a newborn complete physical examination.

[c] Respiratory distress due to meconium syndrome.

[d] Skin lesions: pustulose (N = 1), and ecchymosis (N = 2).

Table 2
Characteristics and course of maternal serum lithium concentrations (mEq/L) at the different extraction time points (from D-3 to D+8) around delivery.

Lithium therapy								
Extraction time point	Dose (mg/d)		[Li] (mEq/L)		[Li] < 0.5 (mEq/L)	Steady state	Pre-dose	Treatment adherence
	N	Mean (SD)	N	Mean (SD)	N (%)	N (%)	N (%)	
D-3 Pregnancy most recent visit	66	993.94 (284.94)	66	0.58 (0.21)	28 (42.40)	66 (100)	66 (100)	Some partial
D-2 Day before hospital birth	66	993.9 (284.94)	26	0.65 (0.20)	8 (30.80)	26 (100)	26 (100)	Some partial
D-1 Admission day for hospital birth	0	_	23	0.59 (0.30)	10 (43.50)	_	_	Some partial
D0 Delivery[a]	41	643.90 (317.84)	64	0.54 (0.26)	33 (51.60)	_	_	Complete
D+1 Postpartum day 1	64	981.25 (288.8)	15	0.61 (0.33)	7 (46.70)	_	15 (100)	Complete
D+2 Postpartum day 2	65	984.62 (296.45)	35	0.63 (0.26)	9 (25.70)	_	25 (100)	Complete
D+3 Postpartum day 3	66	984.80 (302.42)	19	0.73 (0.29)	4 (21.10)	_	19 (100)	Complete
D+4 Postpartum day 4	66	987.88 (295.36)	13	0.71 (0.28)	4 (30.80)	_	13 (100)	Some partial
D+5 Postpartum day 5	66	984.85 (294.70)	5	0.76 (0.29)	1 (20.00)	1 (20)	5 (100)	Some partial
D+6 Postpartum day 6	66	984.85 (294.70)	5	0.59 (0.26)	2 (40.00)	5 (100)	5 (100)	Some partial
D+7 Postpartum day 7	66	984.85 (294.70)	21	0.65 (0.26)	4 (19.00)	21 (100)	21 (100)	Some partial
D+8 Postpartum most recent visit	63	977.78 (294.27)	63	0.65 (0.23)	13 (19.70)	63 (100)	63 (100)	Some partial

[a] Lithium dosage was restarted 6–12 h after delivery.

psychopathologically stable. The mean (SD) time to lithium treatment discontinuation before D0 was 23.61 (13.57) h. Serum lithium concentration at D0 was 0.54 (0.26) mEq/L and 34 women (51.60 %) had a subtherapeutic lithium levels. The mean (SD) time to lithium treatment reinstauration after delivery was 12.22 (8.09) h. Despite the brief interruption in lithium therapy around delivery [37.36 (16.25) h], only four women (6 %) relapsed in the first 7 days postpartum. One of the four woman showed a subtherapeutic serum lithium concentration

(0.41 mEq//L) at delivery and the remaining three women had serum lithium concentration of 0.76, 0.78, and 0.84 mEq/L, respectively. Two women were on lithium monotherapy and two on polytherapy. All presented a mania episode with psychotic features. One from each group (monotherapy vs. polytherapy) required hospitalization. At extraction time point D+8, 11.67 (11.32) days after delivery, 95 % of the total sample ($N = 63$) underwent lithium monitoring in our laboratory. The mean (SD) lithium dose was 977.78 (294.27) mg/day, the mean (SD) serum lithium concentration was 0.65 (0.23) mEq/L, and only 13 from 63 women (19.60 %) of the whole sample had subtherapeutic serum lithium concentrations. In this period (from D-3 to D+8), any women showed serum lithium concentrations higher than 1.50 mEq/L.

Fig. 1A represents the longitudinal pattern of maternal serum lithium concentration around delivery (from D-2 to D+7). We also normalised serum lithium concentrations to the total daily dose in order to accurately compare serum lithium concentrations. See Fig. 1B.

Finally, Table 3 presents comparisons between delivery (D0) and different extractions time points around it (D-2, D-1, D+1 to D+7). We used those data that allowed us to perform a paired data analysis. In a subsample of 22 women, according to the 95 % CI of the mean change, the maternal serum lithium concentrations at D0 were significantly lower than those obtained at D-2 [ϰ mean decrease = 0.19 mEq/L (95% CI: 0.13–0.25)]; this corresponds to a mean relative decrease of 31.7 % (95%CI: 22.3–41.0). After reinstating lithium treatment, the mean absolute and relative increases from D0 to D+2 were 0.1 mEq/L (95%CI: 0.03–0.17) and 33.6 % (95%CI: 13.0–54.3), respectively.

3.3. Lithium placental passage

Table 4A presents serum lithium concentrations in neonates [umbilical cord (UC) or neonate 1ers day of life] and mothers (at D-1 and D0) and corresponding neonates to maternal ratio in all samples and in monotherapy and/or polytherapy.

In 60 mother-infant pairs, intrapartum maternal (D0) venous blood and UC were collected simultaneously to determine serum lithium concentrations. The mean (SD) UC serum lithium concentration was 0.57 (0.26) mEq/L and the mean (SD) D0 serum lithium concentration was 0.54 (0.26) mEq/L. The mean (SD) UC/D0 serum lithium concentration ratio was 1.10 (0.17) indicating complete placental passage. The degree of placental passage was uniform across a wide range of maternal serum lithium concentrations (0.14 to 1.40 mEq/L) and of estimated pregnancy lasts (35^{+6} to 41^{+2} weeks' gestation). There was a strong positive correlation between UC and D0 serum lithium concentration [Pearson correlation coefficient 0.95 (95%CI: 0.91–0.97)], which is visualized in Fig. 2. The UC lithium concentrations exceeded maternal serum lithium concentrations at delivery in 45/60 (75 %) of paired analyses. There was not difference between the UC/D0 serum lithium concentration ratios in lithium monotherapy group [1.11 (0.17)] versus polytherapy group [1.08 (0.17) ($F = 0.428$; $df = 1, 63$; $p = 0.515$)].

Table 4B shows paired maternal and neonatal serum lithium concentrations and corresponding neonatal/maternal ratios in a subgroup of mother-infant pairs ($N = 19$) with lithemias in the three point of extraction: D-1, D0 and UC. The mean (SD) UC/D-1 ratio was 0.97 (0.10) and the mean (SD) UC/D0 ratio was 1.15 (0.12), after a mean (SD) of 25.25 (14.32) h have elapsed since taking the last dose of lithium prior to delivery. In the neonate, the UC serum lithium concentrations exceeded maternal serum lithium concentrations at D-1 in 6/19 (31.58 %), and maternal serum lithium concentrations at D0 in 17/19 (89.47 %) of paired analysis, indicating that lithium elimination was slower in neonates.

3.4. Neonatal characteristics

Table 1 shows the neonatal characteristics at birth. Sixty-four (97 %) neonates were born at term, whereas two neonates (3 %) were spontaneously born late preterm, at 35^{+6} and 36^{+2} weeks of gestation. Ninety-one percent ($N = 60$) of neonates roomed with their mothers on the maternity ward. Fifty-six percent of the neonates ($N = 37$) had acute complications [hypotonia ($N = 15$), hypertonia ($N = 4$), tremors ($N = 8$), sucking difficulties ($N = 4$), systolic murmurs ($N = 8$), respiratory

Table 3
Comparison of maternal mean (SD) serum lithium concentration [Li] (mEq/L) around delivery. Analysis of paired data between different extraction time points (day before hospital birth, admission day for hospital birth, postpartum day 2, 3 and 7) with delivery.

N	Time point of extraction: Delivery (D0) [Li] Mean (SD)	Time point of extraction: Other time points (D-2, D-1, D+2, D+3, D+7) [Li] Mean (SD)	[Li] (mEq/L) ϰ Mean to delivery [95% CI]	% change of [Li] related to delivery [95%CI]
22	**D0** 0.45 (0.23)	**D-2** [a] 0.64 (0.21)	− 0.19 [− 0.25, − 0.13]	−31.7 [− 41.0, − 22.3]
22	**D0** 0.54 (0.29)	**D-1** 0.60 (0.31)	−0.07 [− 0.09, − 0.05]	−12.8 [−16.5, − 9.10]
34	**D0** 0.52 (0.24)	**D+2** 0.62 (0.26)	0.1 [0.03, 0.17]	33.6 [13.0, 54.3]
18	**D0** 0.66 (0.27)	**D+3** 0.72 (0.29)	0.06 [− 0.06, 0.18]	15.0 [− 9.2, 39.2]
19	**D0** 0.59 (0.28)	**D+7** [a] 0.63 (0.26)	0.04 [− 0.10, 0.19]	26.8 [−11.4, 64.9]

Abbreviation: [Li] = Lithium concentration; CI = Confidence interval; D-2 = Day before hospital birth; D-1 = Admission day for hospital birth; D0 = Delivery; D+2 = Postpartum day 2; D+3 = Postpartum day 3; D+7 = Postpartum day 7
Symbol: ϰ = Mean difference.
[q]Serum lithium concentrations were measured at steady-state and 12 ± 2 h post-dose.

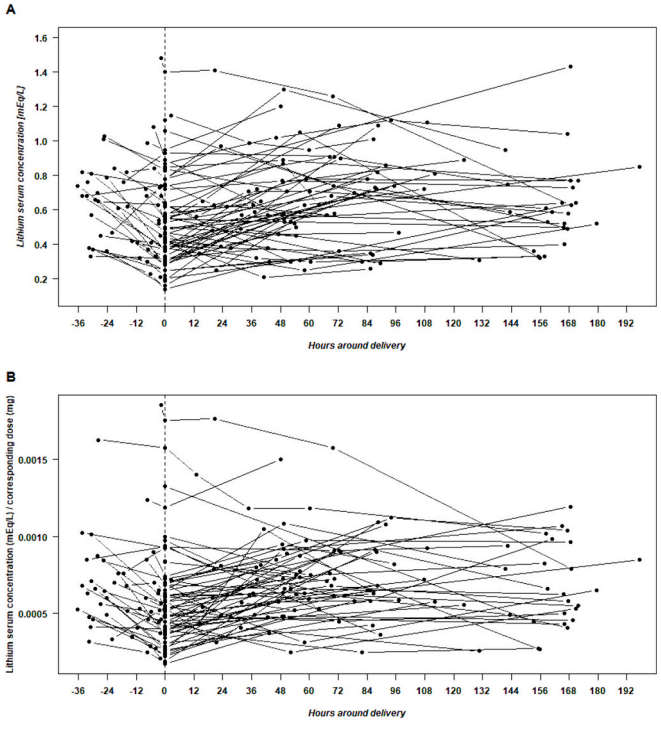

Fig. 1. Course of maternal serum lithium concentration around delivery ($N = 66$). Fig. (A) shows the measured serum concentrations (not adjusted for dose). Fig. (B) shows the same observations after being adjusted for lithium dose. Vertical line represents delivery (delivery = zero h).

Table 4A
Serum lithium concentrations in neonates [umbilical cord or neonate 1er day of life] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and neonatal serum lithium concentration (mEq/L)												
	All cases		Monotherapy		Polytherapy							
					All		Li + AP		Li + AD		Li + AP + AD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
D-1	23	0.59 (0.30)	17	0.61 (0.33)	6	0.55 (0.23)	5	0.62 (0.18)	1	0.23 (0)	0	–
D0	64	0.54 (0.26)	39	0.50 (0.27)	25	0.61 (0.23)	18	0.63 (0.23)	6	0.55 (0.25)	1	0.74
UC	61	0.57 (0.26)	38	0.52 (0.26)	23	0.66 (0.24)	18	0.66 (0.23)	4	0.65 (0.25)	1	0.74
N1	5	0.49 (0.13)	2	0.54 (0.17)	3	0.46 (0.13)	1	0.31 (0)	2	0.54 (0.01)	0	–

Neonatal/Maternal [Li] ratios												
	All cases		Monotherapy		Polytherapy							
					All		Li + AP		Li + AD		Li + AP + AD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
UC/D-1	19	0.97 (0.10)	15	0.97 (0.10)	4	0.99 (0.13)	3	1.03 (0.12)	1	0.87 (0)	0	–
UC/D0	60	1.10 (0.17)	37	1.09 (0.17)	23	1.11 (0.17)	18	1.07 (0.13)	4	1.31 (0.19)	1	1.00
N1/D-1	3	0.83 (0.14)	2	0.82 (0.20)	1	0.84 (0)	1	0.84 (0)	0	–	0	–
N1/D0	4	0.96 (0.26)	2	0.98 (0.30)	2	0.93 (0.33)	0	–	2	0.93 (0.33)	0	–

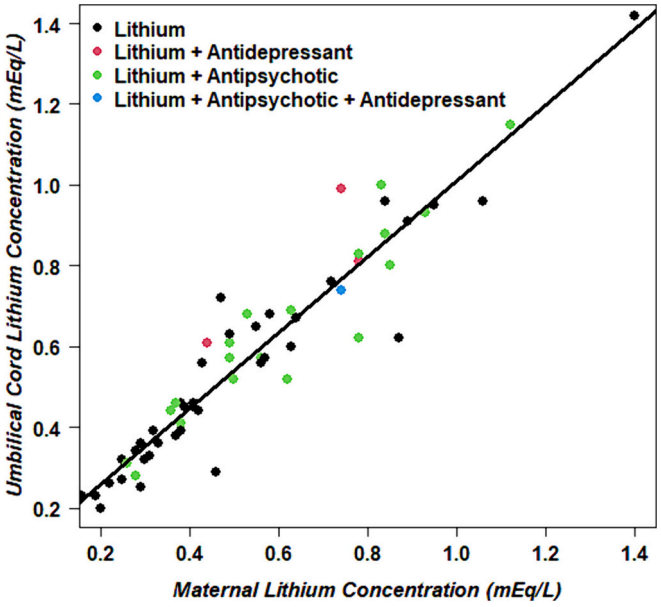

Fig. 2. Joint distribution of maternal and paired umbilical cord serum lithium concentrations at delivery ($N = 60$). Maternal serum lithium concentration and umbilical cord serum lithium concentrations were obtained simultaneously at delivery. Lithium monotherapy ($N = 37$) in black, Lithium + Antidepressant ($N = 4$) in red, Lithium + Antipsychotic ($N = 18$) in green, and Lithium + Antipsychotic + Antidepressant ($N = 1$) in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

distress ($N = 3$), cyanosis ($N = 1$), hepatomegaly ($N = 1$), hyperbilirubinemia ($N = 6$), hypoglycemia ($N = 2$), skin lesions ($N = 3$), and cefalhematoma ($N = 3$)]. In 29 of these neonates the complications were mild and transient and did not need any medical intervention immediately after birth. Five neonates (7.6 %) were admitted to the NICU level II. One neonate due to postnatal aortic coarctation was transferred to another hospital for cardiac catheterization, another required phototherapy due to non-isoimmune hyperbilirubinemia, and three-needed respiratory support due to meconium syndrome. A neonate gave birth in a pediatric monographic hospital with NICU level IV because a prenatal Ebstein's anomaly. Moreover, another neonate presented a microcephaly and cerebral ventriculomegaly, subsequently diagnosed as spastic cerebral palsy of unknown cause. A full overview of neonatal complications with additional neonatal serum lithium concentration at delivery and maternal treatment can be found in Supplementary Table 1.

There were no significant differences between lithium monotherapy ($N = 18/40$) and polytherapy ($N = 13/26$) groups with regard to acute neonatal complications ($p = 0.69$), being neurological complications (hypotonia, hypertonia, tremors, and sucking difficulties) the most frequent in both groups. The mean (SD) hospitalization stay for all neonates attended in the maternity hospital was 3.17 (1.21) days.

3.5. Neonatal serum lithium concentration and acute neonatal outcomes

The neonatal lithium TDM database consisted on 66 neonatal serum lithium concentration measurements: 61 (92.42 %) were obtained from the umbilical cord and 5 (7.58 %) from neonatal vein puncture within 24 h after delivery ($N = 5$, 7.58 %). The mean (SD) umbilical cord serum lithium concentrations ($N = 61$) was 0.57 (0.26) mEq/L, and neonatal vein puncture serum lithium concentration ($N = 5$) was 0.49 (0.13) mEq/L. There were no incidents in the umbilical cord/neonates during blood extraction. See Table 4A.

Hypotonia ($N = 15$) was the most frequently acute neonatal complication of a total of 12 found. It was the only one with at least 10 cases, and it was found to be statistically significantly associated with neonatal serum lithium concentration. The mean (SD) neonatal serum lithium concentration was 0.712 (0.298) mEq/L among neonates with hypotonia compared to 0.534 (0.214) mEq/L among neonates without hypotonia ($t = 2.25$, df $= 60$, $p = 0.028$).

4. Discussion

In this retrospective observational cohort study of 66 mother-infant pairs, we found slightly maternal serum lithium concentration fluctuations after a briefly discontinuation of lithium around delivery. The degree of placental passage was complete across a wide range of maternal serum lithium concentrations and of estimated pregnancy lasts. Neonatal hypotonia was the most frequent acute outcome and, it was associated with neonatal serum lithium concentration.

The human placenta is a complex organ that acts as the interface between maternal and fetal blood circulation. Lithium, with a molecular weight of 7 Da, readily diffuses across the placenta (Griffiths and

Table 4B
Paired serum lithium concentrations in neonates [umbilical cord] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		Monotherapy		Polytherapy							
					All		Li + AP		Li + AD		Li + AP + AD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
D-1	19	0.59 (0.33)	15	0.60 (0.35)	4	0.55 (0.25)	3	0.66 (0.16)	1	0.23	0	–
D0	19	0.53 (0.31)	15	0.54 (0.33)	4	0.48 (0.26)	3	0.60 (0.16)	1	0.14	0	–
UC	19	0.58 (0.31)	15	0.57 (0.33)	4	0.58 (0.37)	3	0.71 (0.11)	1	0.20	0	–
D-1	19	0.59 (0.33)	15	0.60 (0.35)	4	0.55 (0.25)	3	0.66 (0.16)	1	0.23	0	–

Neonatal/Maternal [Li] ratios												
	All cases		Monotherapy		Polytherapy							
					All		Li + AP		Li + AD		Li + AP + AD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
UC/D-1	19	0.97 (0.10)	15	0.96 (0.10)	4	1.02 (0.13)	3	1.08 (0.09)	1	0.86	0	–
UC/D0	19	1.15 (0.12)	15	1.07 (0.09)	4	1.25 (0.15)	3	1.19 (0.12)	1	1.42	0	–

Abbreviations: Li = Lithium; Li + AP = Lithium+antipsychotic; Li + AD = Lithium+antidepressant; Li + AP + AD = Lithium+antipsychotic + antidepressant; D-1 = Admission day to hospital birth; D0 = Delivery (intrapartum); UC = Umbilical cord; N1 = Neonate 1st day of life.

Campbell, 2015). Umbilical cord serum lithium concentrations at delivery, especially when compared to maternal concentrations, provide valuable information about fetal lithium exposure in utero (Bank et al., 2017).

Already, in the late 1960s and early 1970s, several case reports showed that lithium crosses the placental barrier completely (Fries, 1970; Silverman et al., 1971; Weinstein and Goldfield, 1969) or partially (Aoki and Ruedy, 1971; Wilbanks et al., 1970), depending of the time point extraction in mother-infant pairs at delivery. In 1975, Schou and Admisen published a case series (nine new cases and two from the literature) of lithium concentration obtained in mother-infant pair at delivery carried out in different laboratories that indicated that there was a full equilibration on lithium across de placental barrier. More recent, a cohort study (Newport et al., 2005) observed a complete placental passage of lithium across an extensive range of maternal serum lithium concentrations in 10 mother-infant pairs. In a recent retrospective cohort study (Molenaar et al., 2021) showed a strong neonatal/maternal positive correlation in serum lithium concentrations for a wide range of extraction time points around delivery. All these studies were limited by the small sample sizes (Aoki and Ruedy, 1971; Fries, 1970; Molenaar et al., 2021; Newport et al., 2005; Schou and Amdisen, 1975; Silverman et al., 1971; Weinstein and Goldfield, 1969; Wilbanks et al., 1970) or because some samples were not taken in mothers (intrapartum) and neonates (umbilical cord) simultaneously at delivery (Aoki and Ruedy, 1971; Molenaar et al., 2021; Newport et al., 2005; Schou and Amdisen, 1975; Weinstein and Goldfield, 1969; Wilbanks et al., 1970) or lithemias were analysed in different laboratories (Molenaar et al., 2021; Newport et al., 2005; Schou and Amdisen, 1975) or women took different types of lithium formulations (Molenaar et al., 2021), introducing inaccuracies in the index of lithium placental passage. In our study, all lithemias were analysed in the same laboratory and all women were taking lithium carbonate. Our results in a sample between two and six time higher than previously reported (Molenaar et al., 2021; Newport et al., 2005; Schou and Amdisen, 1975) confirm that lithium has a complete lithium placental passage, both in lithium monotherapy and polytherapy.

Due to a decrease in lithium clearance and fluid volume contraction peripartum, maternal serum lithium concentration increased in early postpartum with consequent maternal intoxication risk (Schou et al., 1973; Wesseloo et al., 2017). It has been shown that higher maternal serum lithium concentrations at delivery are associated with more acute neonatal complications (Newport et al., 2005). To minimize the early neonatal risk, different strategies have been proposed along last decades. Some authors have suggested lowering lithium dose by 30–50 % some days before delivery (Goodwin, 2009; Mitchell, 2004). This approaches makes sense, as the neonatal elimination half-life of lithium is around 68–96 h (Mackay et al., 1976; Rane et al., 1978). However, as the elimination half-life of lithium in a young adult is 18–28 h, it could led to an increase in subtherapeutic lithemia (<0.5 mEq/L) with the consequent risk of maternal postpartum relapse. Other authors recommended stopping lithium treatment 24-48 h before a planned hospital birth (caesarean section or induction) or even discontinuing lithium when a woman presents active labouring (Newport et al., 2005; Schou et al., 1973). This approach supposes an average lithemia reduction of 0.28 mEq/L (Newport et al., 2005). Some authors have observed that symptoms worsened in patients when serum lithium concentration decreases abruptly >0.20 mEq/L below their personal baseline concentration and/or below the therapeutic concentration of 0.40 mEq/L (Severus et al., 2008). Finally, the most recent proposed strategy was to careful monitoring serum lithium concentrations around delivery, and to use the maternal lowest effective lithium dose instead of discontinuation in all cases (Deligiannidis et al., 2014). Because, after excluding women with complications or preterm births, there is a considerable variation in gestational lengths (Jukic et al., 2013), this approach needs a close coordination of hospital multidisciplinary team (psychiatric, obstetric, and neonatologist) around delivery (Frayne et al., 2018). Our study showed that maintaining predelivery the minimal individualized effective serum lithium concentration, stopping lithium 12 h before to planned hospital birth, or at hospital admission in active labour, and restarting lithium treatment as soon as the mother is medically stable (6-12 h after delivery), allow to obtain around delivery a mean lithemia fluctuation close to 0.20 mEq/L. We found a small rate of early postpartum relapse, and three of the four women had the lithemia within the therapeutical range.

Knowledge about the potential association between late intrauterine exposure to lithium and early neonatal effects has been limited to case report, case series and small observational studies. Before 2004, around thirty well-documented cases of neonatal toxicity associated with a transient neurodevelopmental deficit after in utero exposure to lithium were published (Kozma, 2005). Most neonates needed supportive treatment between 10 and 14 days improving gradually. Several cases presented paired maternal and neonatal lithemias higher than 1.50 mEq/L, maternal psychiatric decompensation or obstetric complications. In 2005, a study combining a prospective sample of 10 mothers

with 14 cases from previous reports assessed the association of newborn's serum lithium concentration and obstetric and neonatal outcomes (Newport et al., 2005). Neonates were divided in two groups: those with low lithemia (0.20 to 0.58 mEq/L) and those with high lithemia (0.70 mEq/L). The neonates of high lithium exposure group presented an increased risk of lower Apgar scores, higher rates of CNS and neuromuscular complications and longer hospital stays (mean = 10 days), some of them having lithium toxic levels (1.20 to >4 mEq/L) and maternal-obstetric complications. (Aoki and Ruedy, 1971; Arnon et al., 1981; Flaherty and Krenzelok, 1997; Frassetto et al., 1979; Morrell et al., 1983; Nishiwaki et al., 1996; Wilbanks et al., 1970). Subsequently, a retrospective cohort study did not find a significant association between neonatal serum lithium concentrations at delivery (0.05 to 1.16 mEq/L) and neonatal outcomes (Molenaar et al., 2021). However, a high percentage of admissions to medium/high neonatal care (44.8 %) with a median duration of three days, and acute complications (48.3 %), mainly metabolic, were reported during the five postnatal days of protocolized clinical monitoring. Authors interpreted that due to this monitorization period several mild and transient complications were detected might otherwise go unnoticed. Recently, a retrospective cohort study found not differences in acute complications between neonates exposed and non-exposed to lithium, questioning the necessity of neonatal admission with monitoring after lithium exposure (Schonewille et al., 2023). Independently of lithium exposure, and assuming that neonatal lithemias were in the therapeutical range, a 20 % of these neonates were admitted to a neonatal ward monitoring (median stay of three days) due the high obstetric vulnerability of their mothers with bipolar disorders. In our retrospective cohort study, the neonatal serum lithium concentration at birth ranged between 0.20 and 1.42 mEq/L. We observed that half of the neonates had slightly, transient and acute neonatal complications, similar to Molenaar et al. (2021), but ours were mainly neurological. We also found a significant statistical association between neonatal hypotonia and neonatal lithemia >0.75 mEq/L, similar to the high lithium exposure group of Newport et al. (2005) study. Nine percent of our neonates required admission to a NICU (level II or IV) by pediatric indication, with an average stay of three days, due to delivery complications or congenital malformations, a figure smaller than those found in Molenaar et al. (2021) and Schonewille et al. (2023). The results of all these studies, although they did not evaluate causality, indicated that neonatal symptoms should be anticipated after in late intrauterine exposure at any concentration, although lithium toxicity is more likely to occur at high serum lithium concentration. However, this association might be confounded by the occurrence of mood episodes during pregnancy, obstetrical complications, or use of concurrent psychopharmacs.

4.1. Strengths and limitations

As far as we known, this is the largest sample size study analysing the lithium behaviour in mother-infant pairs around delivery and the acute neonatal outcomes after late intrauterine lithium exposure. Strengths of the study were the homogeneity of the sample, the use of a single lithium manufacturer and that all serum lithium concentration measurements were done in a single laboratory. However, the study is not without limitations. It is a retrospective cohort of a sample of healthy uncomplicated pregnancies. For this reason, the results of the study cannot be generalized to all pregnant women treated with lithium. Furthermore, this was a naturalistic study done in real life and we cannot have a paired maternal lithium measurements in each extraction time point at peripartum and in all mother-infant pairs simultaneously at delivery. We do not have data of a cohort control group of women and their neonates of the same characteristics not exposed to lithium treatment, on the same period of follow-up. Finally, sample size was moderate given that there are not big numbers of pregnancies exposed to lithium since we started our standard procedures (De Prisco and Vieta, 2024).

4.2. Implications and conclusions

Appropriate management of lithium treatment around delivery is a difficult balancing act. Lithium equilibrates completely across the placental barrier and maintaining pre-delivery maternal serum lithium concentrations at the minimal individualized effective level and briefly discontinuing lithium at delivery may minimize the risk of maternal and neonatal complications. Additional investigations in bigger samples, prospective design, other perinatal bipolar subgroups and control groups are warranted to better describe the relationship between quantified maternal and fetal lithium exposure near to delivery and maternal and neonatal acute complications.

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CRediT authorship contribution statement

Maria Luisa Imaz: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Mercè Torra:** Writing – review & editing, Validation, Resources. **Klaus Langohr:** Writing – review & editing, Visualization, Supervision, Formal analysis. **Gemma Arca:** Writing – review & editing, Resources. **Dolors Soy:** Writing – review & editing, Resources. **Ana Sandra Hernández:** Writing – review & editing, Resources. **Lluïsa García-Esteve:** Writing – review & editing, Resources. **Eduard Vieta:** Writing – review & editing, Supervision, Conceptualization. **Rocio Martin-Santos:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

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8.3 Artículo 3: resumen estructurado

Imaz ML, Soy D, Torra M., Garcia-Esteve Ll, Soler C, Martín-Santos R. Case report: clínical and pharmacokinetic profile of lithium monotherapy in exclusive breastfeeding. A follow-up case series. Front Pharmacol. 2021; 24: e647414.

FI: 5.6 Cuartil: Q1 Categoría: Farmacología y Farmacia.

Introducción: La mayoría de las directrices recomiendan que las mujeres que toman litio no deben amamantar. La variación en la transferencia es sólo una de las razones detrás de este consejo.

Objetivos: Presentar datos clínicos y farmacocinéticos de nueve parejas de madre-bebé expuestas a monoterapia con litio durante la última etapa del embarazo y lactancia exclusiva en la Unidad de Psiquiatría Perinatal de un hospital universitario (2006-2018).

Método: Obtuvimos datos sociodemográficos, factores de riesgo médicos, variables obstétricas y antecedentes psiquiátricos familiares y personales mediante entrevista semiestructurada, y evaluamos la psicopatología materna con la Escala de Depresión de Hamilton y la Escala de Manía de Young. Un neonatólogo experimentado revisó los resultados neonatales al nacer utilizando la Escala de eventos periparto. Se recogieron muestras pareadas de sangre materna y de cordón umbilical y de sangre venosa infantil. Durante el período de lactancia, monitoreamos las concentraciones séricas de litio y creatinina en pares madre-bebé en el momento del parto y en los días 1 a 5, 7 a 11, 30 y 60 después del parto, y mensualmente hasta los 6 meses.

Resultados: El litio se equilibró completamente en toda la placenta [1,13 (0,10), rango (1,02–1,30)]. Ninguna mujer presentó síntomas de intoxicación por litio en el posparto, dos de los neonatos presentaron hipotonía transitoria (22%). La exposición al litio fue significativamente menor durante la lactancia que durante la última etapa del embarazo, y las concentraciones séricas de litio disminuyeron hasta un 44% con el tiempo desde el parto hasta el primer mes, y hasta un 60% hasta el tercer mes posparto. No hubo crecimiento ni retraso en el desarrollo en el período de seguimiento. Una mujer tuvo un episodio maníaco con características psicóticas a los 45 días posparto.

Conclusiones: En mujeres cuidadosamente seleccionadas con trastorno bipolar, la terapia con litio durante la lactancia puede ser una opción adecuada si se combina con una estrecha monitorización de la pareja madre-hijo.

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Case Report: Clinical and Pharmacokinetic Profile of Lithium Monotherapy in Exclusive Breastfeeding. A Follow-Up Case Series

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Background: Most guidelines advise that women taking lithium should not breastfeed. The variation in transfer is just one reason behind this advice.

Objectives: To present clinical and pharmacokinetic data of nine mother–infant pairs exposed to lithium monotherapy during late pregnancy and exclusive breastfeeding at the Perinatal Psychiatric Unit (2006–2018).

Methods: We obtained sociodemographic data, medical risk factors, obstetric variables, and family and personal psychiatric history by semi-structured interview, and assessed maternal psychopathology with the Hamilton Depression Rating Scale and Young Mania Rating Scale. A senior neonatologist reviewed neonatal outcomes at birth using the Peripartum Events Scale. Paired maternal and cord blood and infant venous blood samples were collected. During the breastfeeding period, we monitored serum lithium and creatinine concentrations in mother–infant pairs at delivery, and at days 1–5, 7–11, 30, and 60 postpartum, and monthly until 6-months.

Results: Lithium equilibrated completely across the placenta [1.13 (0.10), range (1.02–1.30)]. No women presented symptoms of postpartum lithium intoxication, two of the neonates presented transient hypotonia (22%). Lithium exposure was significantly less during breastfeeding than during late pregnancy, and serum lithium concentrations decreased up to 44% overtime from delivery to the first-month, and up to 60% to the third-month postpartum. There was no growth or developmental delay in the follow-up period. One woman had a manic episode with psychotic features at 45 days postpartum.

Conclusions: In carefully selected women with bipolar disorder, lithium therapy when breastfeeding can be an appropriate option if coupled with close monitoring of the mother-infant pair.

Keywords: bipolar disorder, lithium, lactation, case report, pharmacokinetics, exclusive maternal breastfeeding, delivery, nursing infant

INTRODUCTION

Lithium is an effective maintenance treatment for some women with bipolar disorder (Yatham et al., 2018), but there are legitimate concerns about its use during pregnancy and breastfeeding. However, women with bipolar disorder are at high risk of symptom relapse during the perinatal period (Munk-Olsen et al., 2009; Viguera et al., 2011; Wesseloo et al., 2016), and those treated with lithium have a significantly lower rate of relapse during this period (Bergink et al., 2015).

Lithium, a monovalent cation that is absorbed rapidly after oral intake, is not metabolized or bound to proteins and is eliminated almost exclusively via the kidneys. Lithium elimination half-life is about 18–24 h in healthy young women. During pregnancy, serum lithium concentrations decline in relation to the increase in intravascular volume and the glomerular filtration rate (GFR) (Grandjean and Aubry, 2009). Lithium shows complete placental passage and equilibrates between the maternal and fetal circulation across a wide range of maternal concentrations (0.2–2.6 mEq/L) (Newport et al., 2005). Indeed, it has been suggested that the accumulation of lithium in fetal serum may be associated with an increased rate of neonatal complications, sometimes referred to as "floppy baby syndrome" (Kozma, 2005). An association has been observed between high infant lithium concentrations (>0.64 mEq/L), lower 1-min Apgar scores, longer hospital stays, and higher rates of central nervous system and neuromuscular complications (Newport et al., 2005). The regular measurements of the serum lithium concentration are needed perinatally to ensure that it remains within the therapeutic range, and to minimize the risk of both maternal and neonatal complications (Malhi et al., 2017; Wesseloo et al., 2017; Westin et al., 2017). Women are advised to suspend lithium treatment at the onset of labor or for 24–48 h before a scheduled cesarean section (Newport et al., 2005).

During the postpartum period, the maternal serum lithium concentration gradually returns to its preconception level, potentially risking lithium intoxication if women had increased their dose during pregnancy. Lithium is also excreted into breastmilk. Lithium transfer from milk to the infant shows a high variability (20–100%) (Newmark et al., 2019). In infants of mothers receiving lithium maintenance treatment in late pregnancy, and who choose to perform exclusive breastfeeding, two simultaneous phenomena are known to occur in the first weeks of life. On the one hand, it is the elimination of lithium transferred through the placenta, and on the other, is the absorption of lithium transferred through breast milk. Moreover, in front of the infant immaturity of renal function and the increased amount of milk consumption, lithium accumulation and potential intoxication may occur.

Despite the Food and Drug Administration (Food and Drug Administration, 2005) recommending clinical lactation studies for psychopharmaceuticals, data remains limited and uncertainty persists regarding the safe use of lithium during breastfeeding. (The American Academy of Pediatrics (AAP), 2012; Sachs, 2013) has been suggested that lithium can be continued during breastfeeding, provided there is careful monitoring of serum lithium concentrations, as well as renal and thyroid function, in the infant (Viguera et al., 2007). Others recommend only standard pediatric care, including monitoring weight and feeding in the first 2 weeks postpartum (Bogen et al., 2012). However, most international guidelines and some perinatal psychiatrists believe that lithium exposure *via* breast milk could be dangerous and recommend using infant formula (Malhi et al., 2017; Galbally et al., 2018).

Breastfeeding has many important health advantages for both mothers and their children (Rollins et al., 2016; Vitora et al., 2016). The American Academy of Pediatrics (AAP), 2012 recommend exclusive breastfeeding for the first 6 months of life whenever possible, before combining it with complementary foods until the infant is 1–2 years old. Two recent systematic reviews of clinical studies into lithium use during breastfeeding found limited evidence about whether one should initiate, maintain, or discontinue lithium during breastfeeding (Imaz et al., 2019; Newmark et al., 2019).

The aim of this study was to examine serum lithium concentrations in mothers and their exclusively breastfed term infants from delivery.

METHOD

Subjects

We included women with bipolar disorder (DSM-IV or DSM-V) treated with lithium monotherapy, who were clinically stable at least during late pregnancy, and who chose to breastfeed exclusively (N = 9). The patients attended the Perinatal Psychiatry Clinic-BCN Unit between 2006–2018. All gave their written informed consent for the use of paired data from themselves and their infants.

All women were informed of the known risks associated with fetal and infant exposure to lithium during pregnancy and breastfeeding, as well as the risks associated with discontinuing lithium treatment or suffering untreated maternal bipolar disorder, based on current evidence. All women were treated with lithium carbonate, twice at day. The lithium dose was adjusted according to clinical status and serum lithium

concentrations during pregnancy. At 33–35 weeks of pregnancy, the women and their partners devised a birth and breastfeeding plan with a psychiatrist. Women were empirically advised to suspend lithium treatment at the onset of labor in the event of spontaneous deliveries or for 12 h before a scheduled cesarean section or induction. Lithium was restarted 6–12 h after delivery.

Assessments

Mothers

During the first visit during pregnancy, all women completed a semi-structured interview that included questions on their sociodemographic characteristics, medical risk factors, parity, past obstetric complications, and index pregnancy planning. We also recorded any personal and family psychiatric history, substance use, and type of relationship with their partner. A senior psychiatrist administered the validated Spanish versions of the 17-item Hamilton Depression Rating Scale with the Atypical Depression Supplement (Bobes et al., 2003), the Young Mania Rating Scale (Colom et al., 2002), and the Functioning Assessment Short-Test (Rosa et al., 2007) at baseline and follow-up visits. We also reviewed obstetric records to collect information on obstetric risk factors, indication for admission for labor and delivery, method of delivery, and delivery complications. Women were asked about the level of satisfaction with lithium treatment during exclusive breastfeeding period using a visual analog scale (from very poor to very high) at each follow-up visit.

Neonates and Infants

A senior neonatologist reviewed delivery records to collect information on the newborns, from the physical examination performed by the neonatologist at birth (12–24 h of life), admission into a neonatal intensive care unit, and data on neonatal signs obtained with the infant subscale of the Peripartum Events Scale (O'Hara et al., 1986). After hospital discharge infants were evaluated by their pediatrician in accordance with the current standardized clinical protocol (Public Health Agency of Catalonia, 2019).

Blood Sample Collection

During pregnancy routine tests were performed to monitor maternal complete blood counts, glucose levels, and electrolytes; kidney, liver, and thyroid function; serum lithium concentrations; and urinalysis (5 ml) to exclude substance use. Blood samples (10 ml) were collected in the morning before the first daily dose of lithium, at 10–14 h under steady-state conditions.

At delivery, maternal and cord blood samples (10 ml) were collected simultaneously to record serum lithium concentration. At 48–72 h postpartum, a pediatric nurse performed a neonatal screening test to identify any metabolic or endocrine diseases (Public Health Agency of Catalonia, 2013). During postpartum, we monitored lithium and creatinine serum concentrations simultaneously in the mother–infant pairs at 1–5 and 7–11 days, at 1 month, and monthly thereafter while breastfeeding. Two pediatric phlebotomists collected 5 ml of venous blood from the mothers and 2 ml from the infants before the first daily maternal lithium dose. Infant blood analysis was stopped if lithium concentrations in the nursing infant were below the limit of quantification in two consecutive samples, and/or the nursing infant combined with complementary foods, and/or the mother changed to bottle feeding. We also collected a urine sample (5 ml) from mothers to monitor substance use.

Lithium Serum Analysis

For serum lithium analysis, we collected maternal venous blood, cord blood, and neonate/infant venous blood in BD Vacutainer® No-Additive Z Plus tubes (BD Diagnostics, Preanalytical Systems, NJ-07417). Lithium concentrations were determined by an AVL 9180 electrolyte analyzer based on the ion-selective electrode measurement principle (Roche Diagnostics, IN-46256). Two-point calibration was performed every 4 h. The detection limit was 0.10 mEq/L, and the limit of quantification was 0.20 mEq/L. The within- and between-day precisions, expressed as coefficients of variation, were 0.97–4.1% and 1.3–6.4%, respectively. The therapeutical range of lithium has been stablized at 0.5–1.2 mEq/L. The toxic concentration for lithium is ≥ 1.5 mEq/L (Hiemke et al., 2018).

Other Serum Analyses

Serum creatinine levels were measured using the Jaffé method (Modular P, Roche Diagnostics) for traceable measurements, using isotope dilution mass spectrometry. The within- and between-day precisions, expressed as coefficients of variation, were 1.5 and 2.5%, respectively. The modified Schwartz formula (Schwartz et al., 2009), which uses serum creatinine (Scr), height, and an empirical constant [(Kxheight)/Scr]) was used to estimate the neonate/infant GFR. Neonatal thyroid stimulating hormone (TSH) levels were analyzed using the 1,235 AutoDelfia® automatic immunoassay system that used dry blood samples on filter paper (PerkinElmer, Inc.).

Statistical Analysis

All data were analyzed with SPSSv25. A descriptive analysis was performed to characterize the sample and the placental passage of lithium, using the mean and standard deviation (range) for quantitative variables. The ratio of the lithium concentration in umbilical cord to that in maternal plasma was calculated for each maternal–infant pair as an index of the lithium placental passage. In addition, we calculated the within-subject change in lithium serum concentrations for infants from baseline to each assessment point, reporting as mean (standard deviation) and 95% confidence intervals (CIs). We expressed the difference of means results as a percentage of change. We also used within-subject means to examine Pearson correlations between maternal and infant serum lithium concentrations.

RESULTS

Characteristics of the Sample

Table 1 shows the sociodemographic, medical, and obstetric characteristics of each case (N = 9). All women were receiving lithium monotherapy in the third trimester of pregnancy and all were clinically stable. Seven had been taking lithium throughout pregnancy and two had started it during pregnancy, at gestational

TABLE 1 | Maternal characteristics, obstetric outcomes, and treatment during pregnancy.

	CASE-1	CASE-2	CASE-3	CASE-4	CASE-5	CASE-6	CASE-7	CASE-8	CASE-9
Planned pregnancy	Planned happy	Planned happy	Unplanned happy	Planned happy	Accident	Unplanned happy	Planned happy	Unplanned happy	Planned happy
Parity	Primiparous	Multiparous	Primiparous	Primiparous	Primiparous	Primiparous	Primiparous	Primiparous	Multiparous
Medical risk factors[a]	None	None	None	None	None	None	None	None	None
Obstetric risk factors	GD[b]	Mild PE[c] at D	GD[b]/PE wk 38.4	None	None	None	None	None	None
Indication to labor and delivery	None	None	PE	None	None	PROM >12 h	None	None	None
Method of delivery	Vaginal	Vaginal	C-section	Vaginal	Vaginal	Vaginal induction	Vaginal	Vaginal induction	Elective C-Section
Delivery complications	None	None	None	None	None	None	None	None	None
Personal psychiatric diagnosis	BD II	BD nos	BD I	BD I	BD I	BD I	BD I	BD I	BD I
Family psychiatric diagnosis	None	None	None	None	Mother BD I	None	Paternal grandfather BD I	None	None
Lithium (Li) dose (mg/day)	800	800	800	800	800	800	1,200	1,000	1,200–1,600
Li treatment duration	wk25-D	wk0-D	wk0-D	wk0-D	wk36-D	wk8-D	wk0-D	wk8-D	wk0-D
Other medication	FXT wk14-wk28 DZP 5 ad lib	None	LOR 0.5 ad lib ASA 100	CZP 0.5 ad lib	None	ASA 100	None	None	None
Urine drug test[d]	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

Abbreviations: ASA, acetylsalicylic acid; B, baseline (pregnancy first visit); BD, bipolar disorder; C-section, cesarean section; CZP, clonazepam; D, delivery; DZP, diazepam; FXT, fluoxetine; GD, gestational diabetes treated with diet; NA, not available; PROM, premature rupture of membranes; PE, preeclampsia; wk, week.

[a]*Medical risk factors including hypertension, heart disease, endocrine disease, kidney disease, pulmonary disease, gastrointestinal disease, seizure disorder, anemia (Hgb <9.0), extremes of pre-pregnant weight (<45 or >90 kg).*

[b]*Gestational diabetes treated with diet.*

[c]*Protein alteration without clinical symptomatology.*

[d]*Urine drug test included cotinine, benzodiazepines, cannabis, heroin, methadone, cocaine, amphetamine.*

weeks 25 and 36. None were taking medications known to interact with lithium (**Table 1**). Seven women had mean lithium concentrations within the therapeutic range when sampled at steady-state at their most recent prenatal visit 0.79 ± 0.19 (0.50–1.10) mEq/L. Two women did not accept dose adjustments because they were stable during pregnancy and had a history of maintaining lower serum lithium levels without relapse (Cases 4 and 6).

Maternal and Neonatal Serum Lithium Concentrations at Delivery

Supplementary Table S1 details the serum lithium concentrations of mothers and infants from delivery onward. At delivery, serum lithium concentrations were determined from nine maternal samples and eight umbilical cord samples and were 0.41 ± 0.15 (0.19–0.72) mEq/L and 0.44 ± 0.16 (0.23–0.76) mEq/L, respectively. Umbilical cord lithium concentrations exceeded maternal concentrations in all paired analyses. Hematocrit levels at delivery were 36.66 ± 12% (19.60–65.00%) in mothers and 48.24 ± 9.89% (32.80–65.00%) in umbilical cords.

Seven of the nine mothers showed sub-therapeutic (<0.50 mEq/L) lithium concentrations of 0.34 ± 0.09 (0.19–0.43) mEq/L at delivery. The mean time from the last dose to delivery was 28.11 ± 14.59 (12–56) hours. Despite the lower serum lithium concentrations at delivery, the mean daily lithium dose in mothers was 955.56 ± 278.88 (600–1,600) mg/day and the mean infant–mother lithium ratio at delivery was 1.13 ± 0.10 (1.02–1.30). The mothers restarted lithium a mean of 16.33 ± 8.10 (6–31) hours after delivery. Despite the brief peripartum interruption in therapy, none of the women decompensated.

Maternal Satisfaction

Seven women showed a very high level and two moderate level of satisfaction with lithium treatment during exclusive breastfeeding period.

Neonatal Physical Examination at Birth and Neonatal Outcomes

All neonates were full-term, and their outcomes are presented in **Table 2**. Although there were three cases of fetal acidosis at delivery and two cases of transient hypotonia, there were no signs of lithium toxicity or of other adverse clinical events in any infants. We observed a kinking of the ductus in one neonate, which was had resolved by the 2-months follow-up echocardiogram. Another neonate presented an isolated low implantation of the ear auricle.

TABLE 2 | Characteristics of neonates/infants exposed to lithium during late pregnancy and exclusive breastfeeding.

Sex	CASE-1 Female	CASE-2 Male	CASE-3 Female	CASE-4 Female	CASE-5 Male	CASE-6 Male	CASE-7 Male	CASE-8 Male	CASE-9 Female
Gestational age weeks + days	39 + 5	40 + 5	38 + 5	37 + 4	39 + 6	38 + 0	41 + 2	40 + 3	39 + 1
Weight at birth (gr)	3,450	3,520	2,965	3,430	3,324	3,200	3,690	4,100	4,400
Length cm	51.00	51.00	46.00	51.50	50.00	50.00	52.00	53.00	53.00
Head circumference cm	33.00	36.00	35.00	33.00	34.50	34.50	37.00	35.00	37.50
Apgar 1/5/10 min	9/10/10	9/10/10	9/10/10	8/8/9	9/10/10	9/10/10	9/10/10	9/10/10	9/10/10
UA pH	7.24	7.24	7.27	7.22	7.04[a]	7.06[a]	7.27	7.25	7.02[a]
Neonatal TSH[b]	2.56	0.90	1.55	1.85	4.73	1.59	0.58	1.23	2.52
IS-PES neonatal sing (total score)[e]	0	0	0	0	0	0	0	0	[c]
Newborn physical examination (by systems)[d]	Normal	Dysmorphic auricle axial hypotonia	Non-restrictive kinking of the ductus arteriosus	Normal	Normal	Normal	Axial hypotonia	Normal	Systolic murmur I/VI
Weight at 48 h postpartum (gr)	3,195	3,215	2,770	3,200	3,035	3,080	3,270	3,770	3,970
Hospital stay (days)	3	2	4	3	2	2	2	2	3
Exclusive breastfeeding duration (days)	131	36	15	180	17	171	45	123	98
Change of feeding type	Mixed	Infant formula	Infant formula	Complementary	Mixed	Complementary	Infant formula	Complementary	Infant formula
Reasons for termination of breastfeeding	Return to work	Nipple anatomy insufficient breastmilk	Nipple anatomy slow weight gain	Return to work	Slow weight gain	Return to work	Maternal relapse	Infant age	Infant weight crisis during growth

Abbreviations: N = normal; NA = not available; UA pH = umbilical artery pH; TSH = thyroid stimulant hormone; IS-PES = Infant subscale of Peripartum Events Scale.

[a]*Fetal acidosis.*

[b]*Neonatal TSH: neonatal screening at 48 h of life (mU/mL).*

[c]*Hyperbilirrubinemia.*

[d]*Newborn physical examination by systems: skin and lymphatics, head, eyes, ears, nose, mouth and throat, neck-thyroid (goiter), lungs/thorax, cardiovascular (cardiomegaly, bradycardia, systolic murmur); abdomen/hepatic (hepatomegaly, jaundice); neuromuscular (hypotonia, flaccidity, diminished deep tendon reflexes, poor suck, Moro reflexes; central nervous system (lethargy, depression); genitourinary renal (polyuria, diabetes insipidus); respiratory (apnea, cyanosis, labored breathing, need for intubation), ano-genital.*

[e]*IS-PES neonatal sign included 11 items: need for pH correction, volume correction, need for transfusion or plasma exchange, hypoglycaemia, hypocalcemia, hyperbilirrubinemia, treatment for sepsis, meconium aspiration pneumonitis, other serious event, special care admission and treatment to alleviate distress.*

TABLE 3 | Estimated infant lithium serum concentration during exclusive breastfeeding.

Time postpartum	Number of serum lithium analyses available	Mean [Li] (mEq/L)	95% CI (mEq/L)	% Change from baseline	95% CI
Baseline (delivery)	8	0.43	0.32 to 0.55	-	
T1 (3 ± 2 days)	9	0.41	0.33 to 0.49	–6.31	–2.28 to –15.16
T2 (9 ± 2 days)	5	0.29	0.21 to 0.36	–33.45	–24.43 to –42.45
T3 (30 ± 5 days)	6	0.24	0.15 to 0.34	–43.80	–38.35 to –43.88
T4 (60 ± 5 days)	4	0.19	0.12 to 0.27	–54.99	–45.56 to –65.13
T5 (≥90 days)	5	0.18	0.15 to 0.20	–58.52	–38.33 to –78.90

Abbreviations: CI = Confidence interval; T = time.

Maternal and Infant Serum Lithium Concentrations During Breastfeeding

Infants were exclusively breastfed for an average of 93 ± 65.26 (15–189) days (**Table 2**), and 53 samples were obtained from the nine mother–infant pairs between delivery (day 0) and 180 days postpartum (**Supplementary Table S1**). The maternal lithium dose averaged 987 ± 325 (400–1,200) mg/day, with a daily serum concentration of 0.76 ± 0.29 (0.41–1.31) mEq/L. No correlations were observed between maternal and infant serum lithium concentrations (data no shown).

Table 3 shows how infant serum lithium concentrations declined over time from delivery to the third month postpartum, with levels decreasing in the first month of 43.80% (-38.45% to -43.88%), and at three months by 58.52% (95%CI: 38.22% to -78.90%) compared to delivery. The case-by-case data are available in **Supplementary Table S1**. **Figure 1** shows the infant and maternal serum lithium concentrations during lactation.

Supplementary Table S1 shows that umbilical cord creatinine concentrations were similar to those of the mothers at delivery. By 1 week after delivery, all neonates showed a creatinine

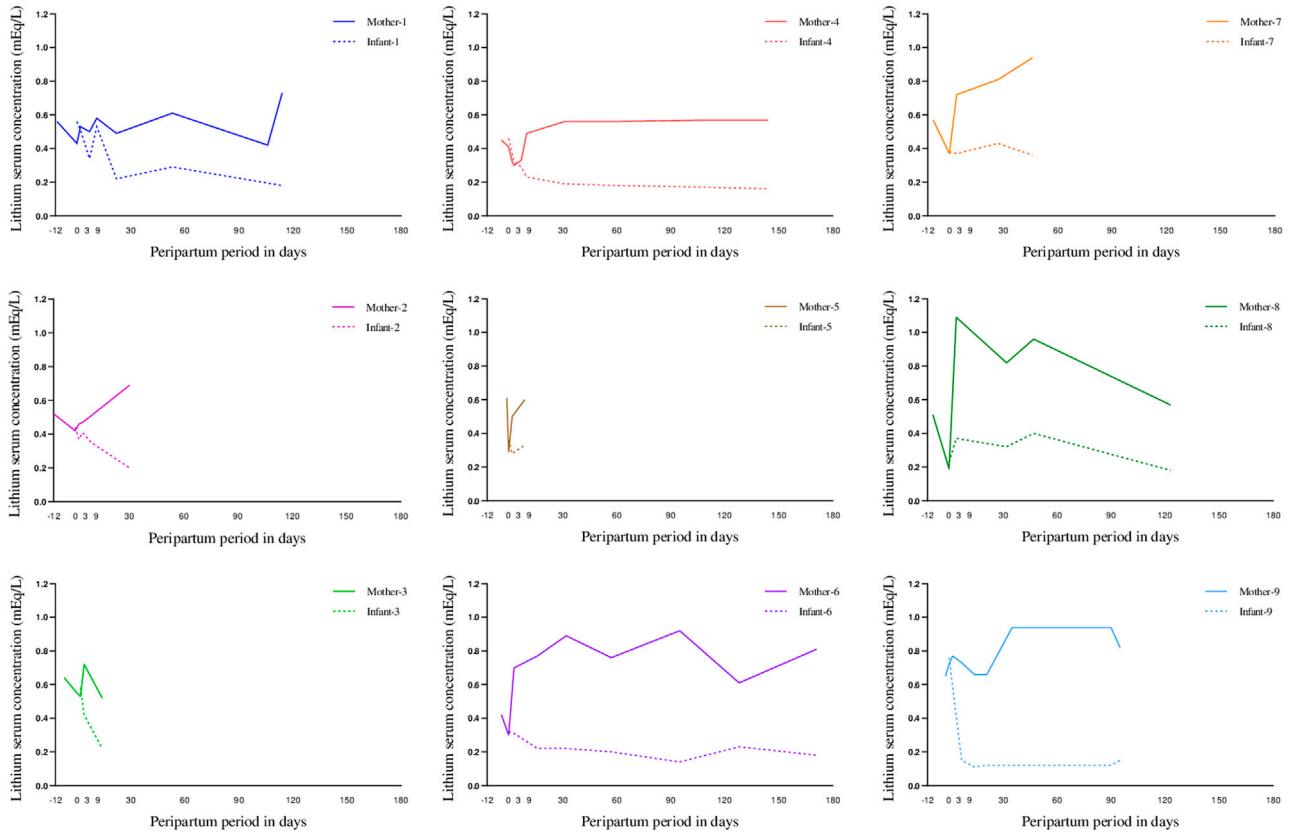

FIGURE 1 | Mother and breastfeed infant lithium serum concentration at delivery and during exclusive maternal lactation case by case (case 1–9). "Day 0" represents delivery.

concentration over normal values (0.35–0.40) mg/dl. The mean neonatal eGFR at delivery was 36.70 ± 12.53 (24.87–64.53) mg/ml/1.73 m^2, which continued to increase to >75 mg/ml/1.73 m^2 with the age of the nursing infant. The mean neonatal TSH concentration was 1.95 ± 1.24 (0.58–4.73) mg/dl, falling within the normal range.

Maternal and Infant Outcomes During Postpartum

At 45 days postpartum, one mother (case 7) experienced a manic episode with psychotic features despite a lithium concentration of 0.91 mEq/L. She was briefly hospitalized for 11 days and breastfeeding was stopped. Finally, no acute growth or developmental delays were reported by the pediatrician in any infant during the follow-up period (data not shown).

DISCUSSION

To our knowledge, this is the first study to have simultaneously examined serum lithium concentrations in both mother and infant from delivery through a period of exclusive breastfeeding. This is surprising given the lack of data supporting advice to stop or avoid lithium during breastfeeding.

A reason lithium is often discouraged is the possible risk of toxicity in nursing infants. Although umbilical cord lithium concentrations were slightly higher than maternal plasma concentrations at delivery, the serum concentration in nursing infants decreased during lactation, independently of the maternal serum lithium concentration. This may be because neonatal hematocrit levels were higher than maternal hematocrit levels at delivery (Lu et al., 1991). Moreover, we observed a smaller reduction in infant lithium concentrations (6%) in the first week of life compared with those that followed. It is likely that this reflects the physiological weight loss typically experienced by nursing infants in their first week (about 10%, mainly due to fluid loss), with lithium clearance being particularly sensitive to changes in fluid volume (Grandjean and Aubry, 2009).

Another reason for discouraging lithium use is the concern of adverse effects on kidney and thyroid function. However, despite elevated neonatal serum creatinine levels in the first few days of life, we observed no lithium-related nephrotoxicity in them while nursing. In full-term neonates, serum creatinine levels are normally elevated at birth, reflecting the mother's kidney function due to fetal-maternal placental equilibration (usually 0.70 mg/dl), and this progressively decreases over several weeks to reflect the infant's true kidney function (Mian and Schwartz, 2017). By contrast, the eGFR (mL/min/1.73 m^2) is physiologically low in the first week of life (5–40 ml/min/1.73 m^2) and continues to increase (up to 65 ml/min/1.73 m^2 by age 2 months), reaching

young adult levels (120–130 ml/min/1.73 m^2) by approximately 2 years (Vieux et al., 2010). In all our cases, neonatal TSH concentrations were within the normal range at 48 h postpartum. We did not analyze TSH concentrations in nursing infants during the lactation period because exposure to lithium was less than that during the fetal period.

Sleep is often interrupted to feed and take care of infants during the first few months postpartum (Lee, 2000). Exclusive breastfeeding might worsen the disruption to sleep patterns (duration and fragmentation) (Doan et al., 2014), and this is an established trigger for relapses, particularly of mania, in women with bipolar disorder type I (Lewis et al., 2017). Women with bipolar disorder who report episodes of mania triggered by sleep loss are also twice as likely to experience an episode of postpartum psychosis (Lewis et al., 2018), with the period of highest risk of psychiatric readmission being 10–19 days postpartum (Munk-Olsen et al., 2009). A recent systematic review and meta-analysis revealed that postpartum relapse rates were significantly lower in women who used prophylactic medication during pregnancy than among those who received none (Wesseloo et al., 2016). In our cases, one woman (11%) had an episode of mania with psychotic features at 45 days postpartum despite a prenatal plan to minimize sleep disruption. This is less than described previously in the literature (Munk-Olsen et al., 2009; Wesseloo et al., 2016).

The study had several limitations. First, it was limited in both size and duration, but it benefited from including a carefully selected sample of clinically stable women with bipolar disorder who had received lithium monotherapy throughout late pregnancy and exclusive breastfeeding. Second, although the findings may not be generalizable to more heterogeneous populations of nursing women with bipolar disorder who are treated with lithium, the results contribute to the accumulating evidence helping clinicians and patients make informed decisions about lithium use during lactation. Third, we did not use a standardized neuropsychological assessment for the nursed infants during follow-up. Finally, we are aware of the limits of detectability of the assay used to measure lithium concentrations, especially for values below the limit of quantification.

CONCLUSIONS

In carefully selected women with bipolar disorder who breastfeed exclusively, lithium can be considered an appropriate option if the infant is monitored closely. Special attention should be given to monitoring clinical features and lithium concentrations in mothers and infants at regular intervals (e.g., 1–5, 7–11, 30, and 60 days postpartum) or if clinical concerns arise. Collaborative studies are needed in larger cohorts to confirm our findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

All gave their written informed consent for the use of paired data from themselves and their infants.

AUTHOR CONTRIBUTIONS

Case study concept and design: MI and RM-S. Psychiatric assessments and ensuring that good clinical practice principles were followed to take care of the bipolar disorder patients: MI. Neonatal outcome assessment: CS. Drafting of the manuscript: MI and RM-S. Acquisition, analysis, or interpretation of the data: MI, MT, DS, CS, LG-E, and RM-S. Critical review of the manuscript for important intellectual content: all authors. Administrative, technical, or material support: MI, MT, and DS.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.647414/full#supplementary-material

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8.4 Artículo 4: resumen estructurado

Imaz ML, Langohr K, Torra M, Soy D, Garcia-Esteve Ll, Martín-Santos R. Neonatal feeding trajectories in mothers wit bipolar disorder taking lithium: pharmacokinetic data. Front Pharmacol. 2021, 22; e752022.

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Introducción: Las mujeres que toman litio durante el embarazo y continúan después del parto pueden optar por amamantar, alimentar con fórmula o combinar estas opciones. El objetivo del estudio fue evaluar las concentraciones séricas de litio neonatal en función de estas tres trayectorias de alimentación.

Método: Seguimos a 24 mujeres con trastorno bipolar tratadas con monoterapia con litio durante la última etapa del embarazo y el posparto (8 por trayecto). Las concentraciones séricas de litio se determinaron mediante un analizador de electrolitos AVL 9180 con un límite de detección de 0,10 mEq/L y un límite de cuantificación (LoQ) de 0,20 mEq/L.

Resultados: Se observó paso placentario completo de litio en el momento del parto, con una relación media entre la concentración de litio en el cordón umbilical y el suero materno de 1,12 ± 0,17. Los tiempos medios hasta el LoQ fueron de 6 a 8, 7 a 8 y 53 a 60 días para la lactancia materna con fórmula, mixta y exclusiva, respectivamente. La prueba de rango logarítmico generalizada indicó que los tiempos medios hasta el LoQ difieren según la trayectoria elegida ($p = 0,037$). Según el análisis multivariado de las concentraciones séricas de litio ajustadas al nacer, los tiempos hasta el LoQ son, en promedio, más prolongados con lactancia materna exclusiva (fórmula, $p = 0,015$; mixta, $p = 0,012$). No se observó acumulación de litio en lactantes bajo lactancia materna exclusiva o mixta. Durante el seguimiento de la lactancia, no hubo retrasos agudos en el crecimiento ni en el desarrollo de ningún recién nacido o lactante. De hecho, las concentraciones de litio en las tres trayectorias disminuyeron en todos los casos. Sin embargo, el tiempo necesario para alcanzar el LoQ fue mucho mayor para aquellas que amamantaban exclusivamente.

Conclusiones: En lactantes no se observó acumulación sostenida de litio ni efectos adversos sobre el desarrollo o crecimiento.

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BRIEF RESEARCH REPORT
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Neonatal Feeding Trajectories in Mothers With Bipolar Disorder Taking Lithium: Pharmacokinetic Data

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Purpose: Women who take lithium during pregnancy and continue after delivery may choose to breastfeed, formula feed, or mix these options. The aim of the study was to evaluate the neonatal lithium serum concentrations based on these three feeding trajectories.

Methods: We followed 24 women with bipolar disorder treated with lithium monotherapy during late pregnancy and postpartum (8 per trajectory). Lithium serum concentrations were determined by an AVL 9180 electrolyte analyser with a 0.10 mEq/L detection limit and a 0.20 mEq/L limit of quantification (LoQ).

Results: There was complete lithium placental passage at delivery, with a mean ratio of lithium concentration in the umbilical cord to maternal serum of 1.12 ± 0.17. The median times to LoQ were 6–8, 7–8, and 53–60 days for formula, mixed, and exclusive breastfeeding respectively. The generalized log-rank testing indicated that the median times to LoQ differ according to feeding trajectory ($p = 0.037$). According to the multivariate analysis-adjusted lithium serum concentrations at birth, times to LoQ are, on average, longer under exclusive breastfeeding (formula, $p = 0.015$; mixed, $p = 0.012$). No lithium accumulation was observed in infants under either exclusive or mixed breastfeeding. During the lactation follow-up, there was no acute growth or developmental delays in any neonate or infant. Indeed, lithium concentrations in the three trajectories declined in all cases. However, the time needed to reach the LoQ was much longer for those breastfeeding exclusively.

Conclusions: In breastfeed infant no sustained accumulation of lithium and no adverse effects on development or growth were observed.

Keywords: bipolar disorder, lithium, breastfeeding, exclusive maternal breastfeeding, mixed breastfeeding, formula feeding, pharmacokinetics, mother-infant dyad

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INTRODUCTION

Breastfeeding is an important public health issue because it promotes health, prevents disease, and contributes to reducing health inequalities in mothers and nursing infants (US Surgeon, 2011). Human milk is tailored to meet the nutritional needs of human newborns and infants, including those who are premature and sick; it provides an optimal balance of nutrients in an easily digestible and bioavailable form (James et al., 2009). Ideally, breastfeeding should be used for the first 6 months of life where possible, followed by a combination of breast milk with appropriate complementary foods until at least 1–2 years (WHO/UNICEF, 2003; AAP, 2012). For this purpose, exclusive breastfeeding is defined as the baby receiving breast milk, with the possible inclusion of vitamins or minerals through drops and syrups (Labbock et al., 2012). Exclusive breastfeeding is the reference model against which all alternative feeding methods should be measured regarding growth, health, development, and other short- and long-term outcomes. However, a common reason for not starting or for interrupting breastfeeding is medication transfer and risk of infant toxicity. Evidence-based perinatal psychopharmacology is driven by the need to balance the disease-related risks (i.e., the natural course of the bipolar disorder) and any risks to the mother, fetus or infant related to the exposure to medication.

Lithium is an effective first-line treatment for bipolar disorder (Yatham et al., 2018). Women who discontinue treatment during the perinatal period are at high risk of relapse (Vigera et al., 2007). Continued lithium prophylaxis during pregnancy may not only maintain mood stability during pregnancy but also prevent postpartum relapse (Poels et al., 2018). Lithium is a monovalent cation that is absorbed rapidly after oral intake, and it is not metabolized or bound to proteins, being eliminated almost exclusively *via* the kidneys (Granjean and Aubry, 2009). Anatomic and physiological changes during pregnancy may progressively alter the pharmacokinetics of lithium over the course of the three trimesters (Feghali et al., 2015; Westin et al., 2017; Allegaert, 2020;). In the third trimester, lithium clearance has been found to rise by 30–50%, which may require an adjustment of the dose guided by therapeutical drug monitoring (Granjean and Aubry, 2009; Wesseloo et al., 2017). Lithium has complete placental passage, with an ion equilibration across placental barrier that is remarkably uniform across a wide range of maternal concentrations (0.2–2.6 mEq/L) (Newport et al., 2005). Due to the very low molecular weight and lack of protein binding, lithium is readily transferred to breastmilk (Hale and Rowe, 2017). Lithium excreted in human breast milk is highly variable, being approximately 50% (range 0.17–1.07%) of the mother serum concentration (Imaz et al., 2019; Newmark et al., 2019). The amount of lithium that receives the infant depends on several factors, such as the volume of milk transfer to the infant, the concentration of the lithium in the milk, and the infant's ability to absorb (Lawrence, 1994). On the other hand, lithium is excreted almost entirely by the kidneys and is freely filtered by the glomeruli. Fractional excretion of lithium is 20%, and 60% of the filtered lithium is reabsorbed in the proximal tubule and 20% in the loop of Henle and the collecting duct (Zhuo and Li, 2013). The tubular secretion is immature at birth and approaches adult values by 7–12 months of age (Zhang et al., 2019). However, the glomerular filtration rate matures more rapidly than tubular secretion, resulting in a glomerutubular imbalance in neonates.

Lithium use while breastfeeding is a controversial topic, due to the potential risk to the neonate of lithium accumulation and secondary toxicity, especially among those who are preterm and sick (Malhi et al., 2017; Galbally et al., 2018). Two systematic reviews of clinical studies into lithium use during breastfeeding found limited evidence about whether one should initiate, maintain, or discontinue lithium during breastfeeding (Imaz et al., 2019; Newmark et al., 2019).

At present, a woman who takes lithium during pregnancy and continues after delivery may choose either breastfeeding or formula feed, or may combine these options. Given the paucity of clinical data on side effects in the infant, pharmacokinetic data may help to assess the safety of breast milk. Infant exposure to lithium is most accurately determined by measuring the drug concentration in an infant's serum (FDA, 2005).

In this study, we hypothesized that lithium would not be accumulated in infants under either exclusive or partial breastfeeding. Our aim was to evaluate neonatal lithium concentrations in different feeding trajectories to help clinicians and patients make informed decisions about lithium use and breastfeeding during lactation.

METHODS

Subjects and Assessments

We included data from 24 women with bipolar disorder who received lithium monotherapy and were clinically stable in late pregnancy in our university hospital between 2006 and 2018. Among these, eight women each were included into three groups, as defined by the World Health Organization (WHO, 2008): exclusive breastfeeding, mixed breastfeeding (i.e., 50–80% breastfeeding) or formula feeding. The participants were required to meet the DSM-IV-R or DSM-V criteria for bipolar I, bipolar II, or bipolar NOS. We also ensured that they were not taking concomitant medication that could interact with lithium (e.g., ibuprofen). The study was approved by the Ethics Committee for Drugs Research of the Institution (CEIm: HCD/2020/1305).

At a prenatal visit (33–35 gestational weeks), consistent with current best practice, all women were informed of the risks and benefits of lithium use during lactation. The patient and psychiatrist then collaborated to write a birth and breastfeeding plan that included clinical management, lithium monitoring in the mother and infant, and strategies to minimise postpartum sleep disruption (i.e., partner/parent support overnight for infant care) (Doan et al., 2014). All women were taking lithium twice a day to maintain constant serum lithium concentrations (Malhi and Tanious, 2011). Women were advised to suspend lithium administration at the onset of labour in the event of spontaneous deliveries, or 12 h before a scheduled caesarean section or induction. Lithium was then restarted at the same dose 6 h after vaginal delivery and 12 h after caesarean section. During subsequent follow-up visits, a senior psychiatrist evaluated the

psychopathological state of the mothers, and adjusted the dose of lithium if necessary.

The neonate underwent standard follow-up. At 12–24 h of life, a neonatologist performed a systematic physical examination; at 48 h, a paediatric nurse performed a screening assessment; and, after hospital discharge, infants were evaluated regularly by a paediatrician (e.g., for weight, length, cranial circumference, neurodevelopment, and vaccination schedule) according to the standard clinical protocol of the Public Health Agency of Catalonia (ASPCAT, 2019).

Blood Sample Collection

At delivery, we collected 10 ml paired samples of cord blood and maternal venous blood. During lactation, two paediatric nurse phlebotomists simultaneously collected venous blood from mothers (5 ml) and infants (2 ml), at 10–11 am, before the mother took her first daily dose of lithium. To study the behaviour of serum lithium concentrations during the lactation period we tried to collect samples on days 2, 7 ± 2, 15 ± 2, 30 ± 5, and 60 ± 5 postpartum; however, this was not always possible due to the technical difficulty involved and the postpartum schedules, and so the time intervals were irregular. There were no adverse incidents in the mothers or neonates/infants during blood extraction. We stopped neonatal/infant blood analysis at the request of the mother, and if serum lithium concentrations were below the limit of quantification (LoQ) of 0.20 mEq/L on two consecutive occasions. The sample at 48 h postpartum was obtained during the newborn screening assessment.

Serum Lithium Analysis

For lithium analysis, we collected maternal, cord, and neonatal/infant venous blood samples in BD Vacutainer® no-additive Z plus tubes (BD Diagnostics, Preanalytical Systems, Franklin Lakes, NJ07417). After allowing the blood to clot in an upright position for at least 30 min, serum was separated by centrifugation at approximately 3,000 rpm for 10 min and analysed as soon as possible. If storage was required, the serum samples were capped and refrigerated at 4°C–8°C until analysis. Lithium concentrations were determined by an AVL 9180 electrolyte analyser based on the ion-selective electrode measurement principle (Roche Diagnostics 9,115 Hague Road Indianapolis, IN46256). Two-point calibration was performed every 4 h with a measurement range between 0.1 and 6 mEq/L. The limit of detection was 0.10 mEq/L and the LoQ was 0.20 mEq/L. Expressed as a percentage (coefficient of variation), the within-day precision was 0.97–4.1% and the between-day precision was 1.3–6.4%.

Lithium Concentration Analysis

The ratio of lithium concentration in the umbilical cord to that in the maternal serum was calculated for each maternal-infant pair as the lithium placental passage index. The infant serum lithium concentration was monitored from birth until the time when the serum lithium concentration reached the LoQ or below. Since lithium could be taken at arbitrary times, the time of interest was interval-censored between the last day that the lithium level was above the LoQ and the first day that it was equal to or below the LoQ.

Statistical Analysis

All data were analysed using SPSS for Windows (Version 25; IBM Corp., Armonk, NY, United States) and the statistical software package R (V4.0.2; The R Foundation for Statistical Computing, Vienna, Austria). A descriptive analysis was performed to characterize the sample and the placental passage of lithium, using either absolute and relative frequencies or means, standard deviations, and ranges as appropriate.

For the analysis of the interval-censored data, we used the Turnbull estimator to estimate the probability that the LoQ was reached as a function of time (Turnbull, 1976). The generalized log-rank test for interval-censored data based on a vector distribution was used to test whether the median times until the LoQ differ among feeding trajectories (Fay and Shaw, 2010; Oller and Langohr, 2017).

To adjust the comparison of the feeding trajectories for the lithium concentrations at birth, the Weilbull regression model was applied. This parametric model models the logarithm of the times of interest assuming that these times follow a Weibull distribution (Gómez et al., 2009). Following, post-hoc comparisons were carried out to compare the feeding trajectories in the frame of this model and the corresponding confidence intervals and *p*-values were adjusted for multiple comparisons.

RESULTS

Characteristics of the Samples

Most participants were Caucasian (96%; $n = 23$), the mean (±SD) age was 33 ± 3.8 years, around half (54%; $n = 13$) had university level education, and all were married or had a partner. Obstetrically, 19 (80%) of the mothers were primiparous and 9 (37.5%) had deliveries by caesarean section. The three study groups (exclusive breastfeeding, mixed breastfeeding, and formula feeding) were similar with respect to sociodemographic and obstetric characteristics.

Two women relapsed postpartum. One woman in the exclusive breastfeeding group needed a brief hospitalization at day 45 postpartum for a manic episode with psychotic features despite having a therapeutic lithium concentration (0.91 mEq/L). Another woman in the mixed breastfeeding group had a manic relapse at 36 days, but with subtherapeutic serum levels (0.21 mEq/L), and her levels improved with outpatient therapy. Breastfeeding was stopped in both patients.

All neonates were full-term newborns (37.4–41.2 weeks) and had an adequate weight for gestional age, mean ± SD (range) 3,478 ± 455 g (2,500–4,400 g). **Table 1** shows the gender and lithium concentrations at delivery for the 24 full-term neonates by their feeding trajectory. As shown, the three study groups were similar with respect to gender and the umbilical cord and maternal lithium concentrations. There was complete lithium placental passage at delivery: the mean ratio of lithium concentration between the umbilical cord and maternal serum was 1.12 ± 0.17. Although most neonates at delivery did not show signs of lithium toxicity or other adverse clinical events, adverse effects were recorded in six (25%). In the exclusive breastfeeding group, there were two cases (25%) of transient hypotonia and one

TABLE 1 | Descriptive statistics of neonates according to feeding trajectory.

	All *N* = 24	Exclusive *N* = 8	Mixed *N* = 8	Formula *N* = 8
Gender				
Female	12 (50%)	4 (50%)	5 (62.5%)	3 (37.5%)
Male	12 (50%)	4 (50%)	3 (37.5%)	5 (62.5%)
Intrapartum serum lithium concentration[a]				
Umbilical cord	0.48 (0.22) (0.23–0.96)	0.44 (0.16) (0.23–0.76)	0.58 (0.29) (0.26–0.96)	0.42 (0.17) (0.25–0.68)
Maternal serum	0.43 (0.20) (0.19–0.95)	0.39 (0.16) (0.19–0.72)	0.50 (0.27) (0.22–0.95)	0.40 (0.15) (0.25–0.64)
Ratio	1.12 (0.17) (0.63–1.53)	1.13 (0.11) (1.02–1.30)	1.16 (0.16) (1–1.53)	1.06 (0.22) (0.63–1.28)

Data are presented as either N (%) or Mean (SD) (range).
[a]*mEq/L, including the ratio of umbilical cord to maternal serum levels.*

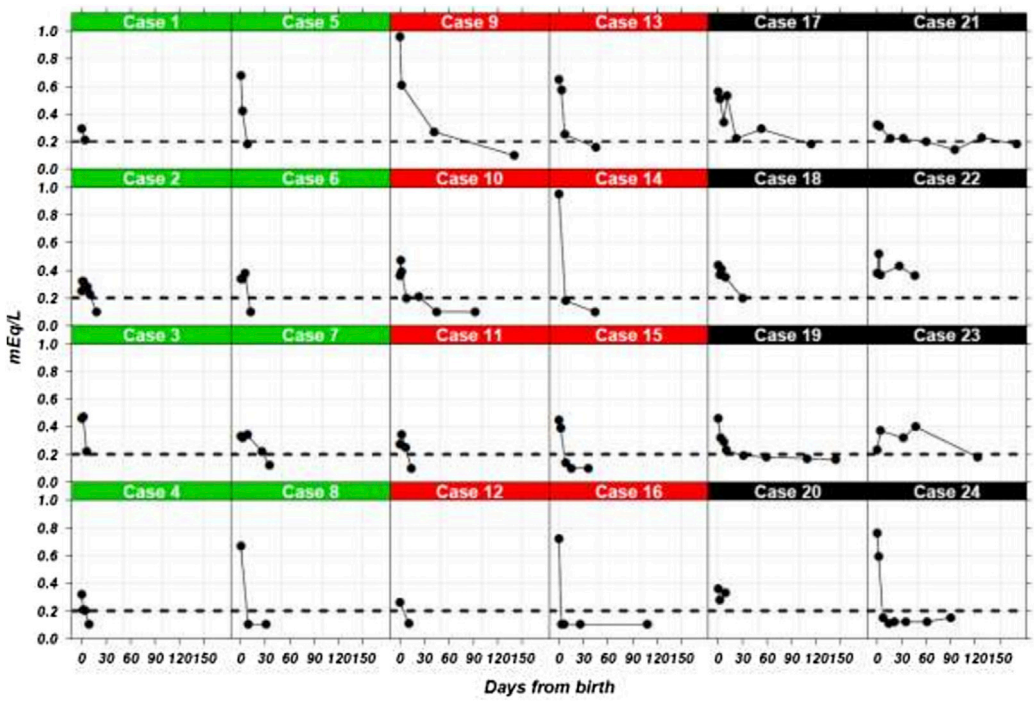

FIGURE 1 | Lithium serum concentrations in 24 neonates from birth. Three groups of neonates are shown by type of feeding. Cases 1–8 (green), 9–16 (red), and 17–24 (black) show the results formula-fed, mixed-fed, and exclusive breastfed neonates, respectively. The dotted line indicates the 0.20 mEq/L limit of quantification.

case (12.5%) of isolated low-set ears. In the mixed breastfeeding group, three (37.5%) had respiratory distress following operative delivery (i.e., forceps or caesarean): one needed neonatal resuscitation in the delivery room (cord lithium, 0.95 mEq/L) and two required admission to the neonatal intensive care unit for 24 h (cord lithium, 0.55 and 0.96 mEq/L). In the formula feeding group, there was a single case (12.5%) of transient hypertonia.

The 48 h newborn screening assessment was in all cases normal. Postpartum neonatal thyroid function (TSH) was between the normal ranges (0.10–5.65 mU/mL) in all cases. Neonatal bilirubinemia results (by transcutaneous bilirubinometers) were below 12 mg/dl (2.50–11.50 mg/dl) in all cases. The physiological weight loss in the first 48 h was 9.3% (8.86–9.76%).

The mean ± SD (range) hospitalisation period was 2.83 ± 0.86 days (2–4 days).

Finally, paediatricians observed no growth or developmental delays in any of the infants during follow-up.

Lithium Concentrations

We collected a total of 138 lithium serum samples, 24 samples from mother-infant pairs at delivery, and 90 samples from neonates during lactation.

Figure 1 shows the time course data of the serum lithium concentrations for each of the 24 neonates, where the dotted line represents the limit of quantification (LoQ) of 0.20 mEq/L. However, seven cases [fourth in formula group (cases 2, 3, 6 and 7), two in the mixed breastfeeding group (cases 10 and 11), and one case in the exclusive breastfeeding group (case 22)] showed a transient increase of serum lithium concentration (<0.15 mEq/L; range: 0.01–0.14) probably associated to the physiological weight loss. In the exclusive

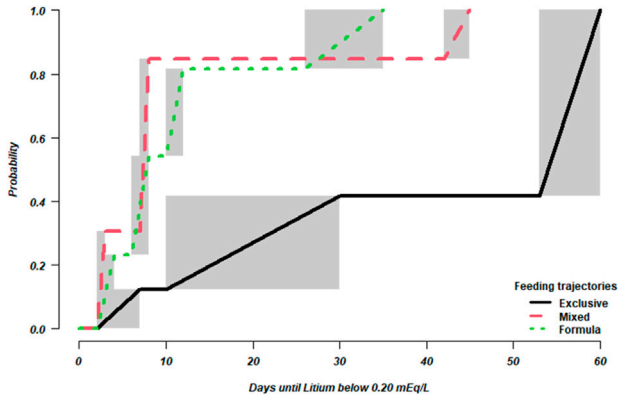

FIGURE 2 | Estimated cummulative probability that lithium serum concentrations falls below LoQ. Shaded areas indicate that the estimation of the probability is not defined in the corresponding intervals, but only known to increase monotonically.

breastfeeding group, one case (case 23) showed also a transient increase (0.14 mEq/L) because of physiological weight loss and drastic increase in maternal level of lithium concentration (0.19 mEq/L to 1.09 mEq/L); and another (case 17) showed an increase of 0.19 mEq/L on the 11th day of life because the infant's serum sample was hemolyzed.

Supplementary Figure S1 presents the interval-censored times until the time when lithium levels fell below the LoQ; the exact moment was not observed and was only known to lie in these intervals. After 40 days, the lithium serum concentration of only 4 neonates with exclusive breastfeeding was definitely below the LoQ, compared to 7 neonates with mixed feeding and 6 with formula feeding.

Univariate Nonparametric Analysis

Figure 2 (and **Supplementary Table 1)** shows the estimated probabilities that the lithium levels falls below the LoQ as a function of time from birth according to the Turnbull estimator. The median times until LoQ lay between 6–8 days (formula feeding), 7–8 days (mixed), and 53–60 days (exclusive breastfeeding). According to the results of the generalized log-rank test to compare the lactation types ($\chi 2 = 6.8$, df = 2, $p = 0.037$) times to LoQ differed between the feeding trajectories.

Multivariate Analysis

Table 2 provides the parameter estimates of the Weibull regression model, which was used to compare the feeding trajectories while adjusting for the lithium concentrations at birth, and shows the results of the pairwise post-hoc comparisons. The differences observed among breastfeeding trajectories are not explained by different lithium levels at birth and we can therefore state that, on average, the times to LoQ were longest under exclusive breastfeeding; no statistically significant differences were found between the mixed and the formula trajectory.

DISCUSSION

As far as we know, this is the first study to compare serum lithium concentrations during three feeding trajectories after delivery: namely, exclusive breastfeeding, formula feeding, and a mixed approach. Notably, no lithium sustained accumulation was found in infants under either exclusive or mixed breastfeeding. As expected, however, we found significant differences in the time taken to reach or exceed the LoQ between the feeding trajectories. All in all, the results provide substantial support for recommending maternal breastfeeding in women with lithium-responsive bipolar disorder in whom lithium prophylaxis helps to prevent postpartum affective relapse.

In a preliminary study of exclusive breastfeeding in the neonatal period, we found that lithium clearance in nursing infants was independent of maternal lithium levels, and that infant serum lithium concentrations fell over time from delivery to the third month postpartum, by 43.80% (95%CI: −38.45% to −43.88%) in the first month and by 58.52% (95%CI: −38.22% to −78.90%) at 3 months (Imaz et al., 2021). In women who had taken lithium weeks before delivery, it was shown that infant

TABLE 2 | Parameter estimates of the Weibull regression model for time until lithium serum concentrations falls below LoQ and pairwise post-hoc comparisons of feeding trajectories.

Weibull regression model				
—	**Value**	**SE**	**Z**	**p**
(Intercept)	3.566	0.582	6.126	0.000
Lithium concentration[a] at birth	0.851	1.117	0.762	0.446
Mixed *vs* exclusive breastfeeding	−1.593	0.637	−2.501	0.012
Formula *vs* exclusive breastfeeding	−1.357	0.555	−2.444	0.015
Pairwise comparisons				
—	**Differences**	**Lower 95%CI**	**Upper 95%CI**	**p**
Mixed *vs* exclusive breastfeeding	−1.593[b]	−3.085	−0.102	0.033
Formula *vs* exclusive breastfeeding	−1.357[b]	−2.656	−0.057	0.038
Formula *vs* mixed breastfeeding	0.237	−1.284	1.757	0.929

Abbreviations: CI, confidence interval; SE, standard error

[a]*mEq/L.*

[b]*The negative sign indicates larger times until lithium serum concentrations falls below LoQ under exclusive breastfeeding.*

serum concentrations in the first week postpartum may reflect transplacental passage rather than intake *via* breast milk (Hale and Rowe, 2017). In the present study, we compared the pharmacokinetics of serum lithium concentrations from delivery during three feeding trajectories. The analysis of the formula feeding trajectory (in which the last infant exposure to lithium was at delivery) provided us with a reference point with which to compare the course of the exclusive and mixed breastfeeding trajectories in the first 7–10 days postpartum. Although serum lithium concentrations declined in all three trajectories, the time needed to reach the LoQ was longest in the exclusive breastfeeding trajectory. The non accumulation of lithium in breastfeeding infant could be explained by 1) the decrease of transport of lithium into the milk with age; and 2) because the neonatal lithium renal excretion increases with maturation of renal tubular transport, even though tubular function matures more slowly than glomerular function after birth (Zhang et al., 2019).

Previous systematic reviews have failed to address clinical symptoms of lithium toxicity in infants for levels <0.30 mEq/L (Pacchiarotti et al., 2016; Imaz et al., 2019; Newmark et al., 2019). We decided to stop monitoring lithium concentrations in infants when levels reached ≤0.20 mEq/L in two consecutive determinations (i.e., the LoQ) (Armbruster and Pry, 2008). We chose the time to reach the LoQ as our outcome variable because the three groups had different lithium exposures: the last exposure was at delivery in the formula group, but it continued in different proportions in the mixed and exclusive breastfeeding groups. However, neonates in all groups shared the problems of an immature renal system and the physiological loss of fluids, which may affect lithium concentrations.

With regard to the effects of transplacental lithium exposure at birth, six neonates in this sample suffered mild and transient complications that resolved before hospital discharge. During the follow-up period, paediatricians found no observable growth or developmental delay in neonates or infants in any of the three trajectories.

The postpartum period is associated with the highest lifetime risk of hospitalisation for women with bipolar disorder (Munk-Olsen et al., 2009). Lithium has proven to be an effective preventive treatment during the postpartum period (Berking et al., 2015). A systematic review and meta-analysis showed a relapse rate during postpartum in women with bipolar disorder of 37% (Wesseloo et al., 2016). In the first month postpartum, the recommended therapeutical range is ≥0.80 mEq/L (Wesseloo et al., 2017). In our sample of bipolar disorder patients under lithium monotherapy during lactation, only two patients out of 24 (fewer than 10%) relapsed during follow-up (at 36 and 45 days postpartum respectively): one with a subtherapeutic serum lithium concentration, and the other within the therapeutic range.

The study has several strengths and limitations. The strengths include its assessment of the three breastfeeding trajectories from delivery in groups with similar obstetrical and demographic characteristics. As for to limitations, the study was performed in a selected sample of bipolar women receiving lithium monotherapy during pregnancy and lactation, all of whom had full-term newborns. As such, our findings may be not generalizable to more heterogeneous populations (i.e. pre-term neonates; sick infants; lithium in polytherapy, and so on). The amount of lithium transferred to breastfed infant could be measure directly in infant serum or estimated on the basis of pharmacokinetics parameters [i.e. milk to maternal plasma drug concentration ratio (M/P ratio), the relative infant dose (RID)]. The infant serum concentration provides information regarding the fraction of drug that is systematically available to the breastfed child (Begg et al., 2002). It is the most direct measure for risk assessment (FDA, 2005). We decided to use the infant serum lithium concentration as direct measure. Having to obtain a blood sample to analyze the infant serum lithium concentration may be a limitation, as this is an invasive method that may cause pain and may be rejected by some parents. Because of this, the determination of lithium in saliva has been proposed; however, from the pre-analytical point of view, obtaining saliva in infants between 0 and 2 months is especially challenging, and in addition the therapeutic range of lithium in this matrix has not been yet defined (Murru et al., 2017). We were also aware of the limit of detectability of the assay used to measure lithium concentration, especially for values below the LoQ.

CONCLUSIONS

We conclude that bipolar women treated with lithium monotherapy during late pregnancy (with a brief peripartum discontinuation) and postpartum may continue lithium use during breastfeeding, since it is safe and does not cause infant harm or accumulation of lithium in our sample. Lithium concentrations in the three lactation trajectories (exclusive, mixed and formula) fell in all cases. However, the time needed to reach the LoQ was much longer in the case of mothers who breastfed exclusively.

Clinical follow-up is required throughout the postpartum period to ensure the safety of both the mother and infant. We recommend that infant lithium serum concentrations be monitored peripartum at 2 days and 1 week postpartum for all trajectories, with additional monitoring at 1 and 2 months postpartum for those who exclusively breastfeed. Later on, if infant lithemia is < 0.20 mEq/, lithium monitoring may only be necessary in the case of fever, unusual behaviour, increased sedation, hypotonia, dehydration, difficulty feeding, or abnormal growth or development.

Finally, more standardized and collaborative studies are needed in larger cohorts to better elucidate the extent of maternal-infant lithium transfer and the effects of breast milk exposure on infant health and development.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics committee of drugs research of Hospital Clinic de Barcelona, Spain. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors (MLI, KL, MT, DS, LG-E, and RM-S) gave substantial contributions to the interpretation of the data, revised the manuscript critically and approved the final version. MLI and RM-S designed the study and wrote the first draft of the paper. Specific contribution: MLI recorded the retrospective data of the patients. KL implemented the statistical methods. KL, MLI, and RM-S performed the data analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.752022/full#supplementary-material

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9 DISCUSIÓN

El litio es el fármaco más efectivo para estabilizar el ánimo y es un tratamiento de primera línea para el trastorno bipolar. Es considerado por muchos autores como el patrón oro para el tratamiento del trastorno bipolar durante el embarazo y posparto. Comparado con otros tratamientos de mantenimiento, el litio ofrece la mejor ratio eficacia/seguridad tanto para la madre como para el feto/recién nacido. El litio utilizado durante el primer trimestre del embarazo se ha asociado a malformaciones congénitas, aunque en menor medida que las descritas inicialmente (99). El litio es más efectivo como tratamiento de mantenimiento del trastorno bipolar y para prevenir la psicosis posparto (47, 45) que otros fármacos como la lamotrigina o los antipsicóticos (123, 124, 125).

Sin embargo, el litio es un fármaco que necesita ser dosificado de forma cuidadosa ya que posee un margen terapéutico estrecho. En la práctica clínica es preciso realizar una monitorización de sus niveles de concentración sérica que deben mantenerse entre >0,6 mEq/L y <1,2 mEq/L para evitar niveles subterapéuticos (<0,4 mEq/L) y niveles de riesgo tóxico (>1mEq/L), respectivamente. Además, dado que su eliminación es prácticamente renal, es importante evaluar la función renal, la depleción de sodio y la deshidratación. También hay que evaluar el riesgo de interacción con otros fármacos como pueden ser los antiinflamatorios no esteroideos, así como las complicaciones obstétricas durante el embarazo y parto (94, 96). Durante el embarazo como hemos comentado en la introducción se produce de forma fisiológica un incremento de la filtración glomerular (GRF) que conlleva una disminución de las concentraciones séricas de litio con el consiguiente incremento del riesgo de recaída.

Debido a los escasos datos sobre el comportamiento farmacocinético del litio durante el periodo perinatal, las recomendaciones sobre la monitorización del litio y el ajuste de dosis en este período son también limitados. Ello motivó nuestro interés en el tema y nos llevó a estudiar de una cohorte retrospectiva de mujeres tratadas con litio durante el período perinatal (preconcepción, embarazo y primer año postparto) que incluyó 1326 determinaciones analíticas de creatinina sérica y 1260 determinaciones

analíticas de litio, correspondientes a 109 embarazos de un total de 95 mujeres. Ésta es la mayor cohorte en la que se ha realizado un estudio observacional retrospectivo sobre el comportamiento longitudinal del litio y de la creatinina durante el periodo perinatal. Nuestros resultados mostraron que el primer y segundo trimestre del embarazo se caracterizaba por una disminución significativa de las concentraciones séricas del litio con riesgo de niveles subterapéuticos, mientras que en el tercer trimestre de embarazo y en el posparto, las concentraciones fueron incrementándose gradualmente hasta llegar al nivel preconcepcional.

Nuestros hallazgos están en línea con estudios previos (94, 100, 104, 126) que han mostrado, comparado con el periodo preconcepcional, que la concentración de litio disminuye a lo largo del embarazo. De forma similar al estudio de Wesseloo y cols. (2017) (104), la concentración sérica de litio se incrementa ligeramente en el tercer trimestre de embarazo, pero se observa que este aumento se mantiene por debajo de la línea basal preconcepcional, incrementándose durante el posparto. Nuestros resultados muestran la importancia de monitorizar las concentraciones séricas de litio debido a la disminución de la litemia.

Por otro lado, tal y como hipotetizamos, las concentraciones séricas de litio y de creatinina mostraron un patrón longitudinal muy parecido a lo largo del periodo perinatal. Tal y como realizamos en nuestro estudio, las evaluaciones de las concentraciones séricas de creatinina y litio durante el embarazo pueden ser muy útiles para descartar alteraciones de la litemia debidas a cambios en la función renal durante el embarazo versus cambios producidos por otros factores como la no adherencia al tratamiento.

Muchas de las mujeres en nuestro estudio, tomaban el litio en dos o más veces al día durante el embarazo para minimizar el pico de concentraciones de litio (127). Observamos que una elevada proporción de mujeres tenía sus concentraciones séricas de litio por debajo de <0.4 mEq/L durante el periodo perinatal, cercana al 40% en el primer y segundo trimestre del embarazo. Fue durante el segundo trimestre del embarazo cuando las mujeres recibieron de su psiquiatra la prescripción media más alta de litio. Sin

embargo, ninguna de estas mujeres con niveles subterapéuticos presentaron una recaída del trastorno bipolar. Mejorar la adherencia al tratamiento durante el embarazo es un auténtico reto. Es sabido que las mujeres durante este periodo tienen a tener peor adherencia a cualquier tratamiento farmacológico. Un adecuado consejo preconcepcional puede atenuar la percepción incorrecta de la seguridad del tratamiento con litio y otros fármacos en las mujeres embarazadas. En nuestra muestra el 40% de las mujeres de la cohorte había recibido consejo preconcepcional. Por otro lado, la adherencia al tratamiento mejoró en el tercer trimestre del embarazo, periodo cercano al parto. Otro grupo de mujeres embarazadas con riesgo clínico fue aquel cuyas litemias eran >1.0 mEq/L en el embarazo, que en algunos casos puede deberse a complicaciones obstétricas.

La placenta humana es un órgano complejo que actúa como interfaz entre la circulación sanguínea maternal y fetal. El litio, con un peso molecular de 7 Dalton se difunde rápidamente a través de la placenta (128). La concentración de litio en el cordón umbilical en el momento del parto proporciona una información valiosa acerca de la exposición fetal al litio, especialmente cuando se compara con las concentraciones maternas de litio (13). A finales de los años 60 y principios de los años 70 del siglo pasado, se publicaron diversos casos clínicos que mostraban que el litio atravesaba la barrera placentaria de forma completa (129-131) o de forma parcial (132, 133) dependiendo del momento en que se realizara la litemia en la madre y en el recién nacido durante el parto. En 1975, Schou y Admisen (134) publicaron una serie de casos (nueve casos nuevos y dos extraídos de publicaciones científicas previas) en los que las concentraciones de litio obtenidas en la diada madre-hijo en el parto, analizadas en diferentes laboratorios, indicaban que el litio se equilibraba de forma completa a través de la barrera placentaria. Mas recientemente, Newport y cols. (2005) (101), en un estudio de cohortes de 10 díadas madre-hijo observaron que la transferencia placentaria era completa para un rango amplio de litemias. Un reciente estudio de cohortes retrospectivo (135) ha mostrado una que existe una estrecha correlación positiva entre las litemias neonatales y maternas para un amplio rango de puntos de extracción alrededor del parto.

Todos estos estudios a los que hemos hecho referencia en el párrafo anterior presentaban una serie de limitaciones como son un tamaño muestral pequeño (101, 126,

129-135), algunas de las muestras no fueron obtenidas en la madre (intraparto) y en el recién nacido (cordón umbilical) de forma simultánea en el parto (101, 126, 131-133, 135), las litemias fueron analizadas en diferentes laboratorios (101, 126, 135), o las mujeres fueron tratadas con diferentes formulaciones de litio (134), introduciendo pequeñas inexactitudes en el índice de la transferencia placentaria del litio. En nuestro estudio todas las litemias fueron analizadas en el mismo laboratorio y todas las mujeres fueron tratadas con la misma formulación (carbonato de litio). Nuestros resultados provienen de una muestra entre dos y seis veces mayor que los estudios previos (101, 126, 78, 135) confirmando que el litio presenta una transferencia placentaria completa tanto en tratamiento de litio en monoterapia o en politerapia.

Debido a disminución del aclaramiento de litio y a la contracción del volumen de líquidos en el periparto, se produce un incremento de la litemia maternal en el posparto inmediato lo que conlleva a un incremento del riesgo de intoxicación materna por litio (104, 126). Está descrito que las litemias maternas elevadas en el parto se asocian con un mayor número de complicaciones agudas neonatales (101). Para minimizar el riesgo neonatal temprano se han propuesto diferentes estrategias a lo largo de las últimas décadas. Algunos autores han sugerido disminuir la dosis de litio en un porcentaje entre un 30-50% unos días antes del parto (136, 137). Esta aproximación tiene sentido ya que la vida media de eliminación del litio en el neonato es cercana a 68-96 horas (138, 139). Sin embargo, como la vida media de eliminación del litio en el adulto joven es de 18-28 horas, esta estrategia puede dar lugar a un incremento de las litemias subterapéuticas (<0.5 mEq/L) con el consiguiente riesgo de una recaída materna en el posparto. Otros autores recomiendan interrumpir el tratamiento con litio entre 24 y 48 horas antes de un parto programado (mediante inducción o cesárea programada) o la discontinuación del tratamiento con litio cuando la mujer inicia el trabajo del parto (101, 126). Esta aproximación supone una reducción media de la litemia materna de 0.28 mEq/L (101). Algunos autores han observado un empeoramiento sintomático en pacientes después de una disminución brusca de la litemia de más de 0.20 mEq/L por debajo de su litemia basal y/o una disminución de la litemia por debajo de 0.40 mEq/L (140). Finalmente, la estrategia que se ha propuesto más recientemente es la realizar una estrecha monitorización de la litemia materna alrededor del parto, utilizando la menor dosis efectiva materna de litio, en lugar de discontinuar el litio en todos los casos (3). Dado

que, tras excluir mujeres con complicaciones o partos pretérmino, se observa una gran variabilidad en la duración del embarazo (141), esta aproximación precisa de un importante nivel de coordinación multidisciplinar hospitalaria (psiquiatra, obstetra, y neonatólogo) (142). Los resultados de nuestro estudio muestran que el mantenimiento preparto de la litemia mínima efectiva para cada mujer, la supresión del tratamiento con litio 12 horas antes de un parto programado o tras el ingreso hospitalario en trabajo de parto, junto a la reinstauración del tratamiento con litio 6-12 horas después de parto, supone en el periparto una fluctuación media de la litemia materna de alrededor de 0.20 mEq/L. En nuestra muestra observamos una pequeña tasa de descompensación psicopatológica materna en el postparto temprano, en la que tres de las cuatro mujeres que se descompensaron presentaban una litemia dentro de rango terapeútico.

El conocimiento sobre la potencial asociación entre la exposición intrauterina a litio y los efectos neonatales agudos se limita a la publicación de casos aislados, de serie de casos y de pequeños estudios observacionales. Antes del 2004, habían sido publicados cerca de 30 casos bien documentados de toxicidad neonatal asociado a déficits transitorios en el neurodesarrollo tras la exposición uterina al litio (102). La mayoría de los neonatos necesitaron tratamiento de soporte entre 10 y 14 días con una mejoría gradual. Varios de estos casos presentaban litemias maternas y neonatales determinadas simultáneamente por encima de 1,50 mEq/l, recaídas psiquiátricas maternas o complicaciones obstétricas. En 2005, un estudio que combinaba una muestra prospectiva de 10 madres con 14 casos publicados previamente evaluó la asociación entre la litemia neonatal y resultados neonatales y obstétricos (101). Para ello los neonatos fueron divididos en dos grupos: aquellos con litemias bajas (0.20-0.58 mEq/L) y aquellos con litemias altas (>0.70 mEq/L). Los neonatos con litemias altas presentaban un incremento del riesgo de tener puntuaciones bajas de Apgar, más complicaciones neuromusculares y estancias hospitalarias mayores (estancia media de 10 días), algunos con litemias en niveles tóxicos (1,20 mEq/L – 4,00 mEq/L) y complicaciones obstétricas maternas (132, 133, 143-147). Posteriormente, un estudio de cohorte retrospectivo no encontró asociación estadísticamente significativa entre las litemias de los neonatos en el parto (0.05 mEq/L -1,16 mEq/L) y los resultados neonatales (135). Sin embargo, dicho estudio observó durante el seguimiento postnatal protocolizado durante los primeros 5 días de vida un elevado porcentaje de admisiones en unidades de cuidados intermedios /intensivos

(44,8%), una estancia media de tres días, y complicaciones agudas (48,3%), principalmente metabólicas. Los autores apuntan a que, debido a este período de monitorización, se detectaron y notificaron complicaciones neonatales leves y transitorias que de otra manera habrían pasado desapercibidas. Recientemente, otro estudio de cohorte retrospectivo no encontró diferencias en las complicaciones agudas entre los neonatos expuestos y no expuestos a tratamiento con litio, cuestionando la necesidad de monitorizar en régimen de ingreso a los neonatos expuestos a litio (54). Independientemente de la exposición a litio y asumiendo que las litemias neonatales estuvieran en el rango terapéutico, un 20% de estos neonatos fueron admitidos a una sala de monitorización neonatal (estancia media de 3 días) debido a la alta vulnerabilidad obstétrica de las madres con trastorno bipolar. En nuestra cohorte retrospectiva, la litemia neonatal al nacimiento se situó en un rango de 0,20 mEq/L y 1,42 mEq/L. Observamos que la mitad de los neonatos presentaban ligeras complicaciones agudas transitorias, de forma similar a las descritas por Molenaar y cols. (2021) (135), aunque en este caso eran principalmente neurológicas. También encontramos una asociación estadísticamente significativa entre la hipotonía neonatal y la litemia neonatal mayor de 0.75 mEq/L, semejante a la encontrada por Newport y cols. (2005) (101) en el subgrupo de neonatos con litemias superiores a 0, 70 mEq/L. El nueve por cien de nuestros neonatos requirieron un ingreso en la unidad de cuidados neonatales (UCIN, nivel II o IV) por indicación de neonatología, con una estancia media de 3 días, debido a complicaciones neonatatales asociadas al parto o a malformaciones neonatales congénitas. Este porcentaje de ingreso fue menor que el encontrado en el estudio de Molenaar y cols. (2021) (135) y Schonewille y cols. (2023) (54).

Tomadas en conjunto todas estas evidencias, aunque estos estudios no evalúan causalidad, si parecen indicar que debe anticiparse la presencia de síntomas agudos neonatales tras exposición intrauterina a litio en cualquier concentración sérica, si bien la toxicidad por litio es más frecuente que ocurra con litemias elevadas. Sin embargo, la presencia de fases afectivas durante el embarazo, las complicaciones obstétricas y el uso concomitante de otros psicofármacos pueden actuar como factores confusores.

Tras realizar una revisión sistemática sobre el uso del litio durante la lactancia (148), en nuestro estudio constatamos que existían escasas evidencias que apoyaran la indicación clínica de suspender o evitar el tratamiento materno con litio durante la lactancia. La razón por la que a menudo se desaconseja su utilización durante este periodo es por el posible riesgo de toxicidad neonatal. En nuestro estudio sobre lactancia materna exclusiva en mujeres lactantes tratadas con litio en monoterapia durante el tercer trimestre de embarazo y en el posparto (N=9), si bien las concentraciones séricas de litio en el cordón umbilical fueron ligeramente más elevadas que las maternas en el momento del parto, las litemias en los recién nacidos disminuyeron a lo largo del período lactancia independientemente de las litemias maternas. Esto podría ser debido a que en el momento del parto los niveles de hematocrito neonatal son más elevados que los maternos (149). En nuestro trabajo observamos además que el porcentaje de disminución de las litemias neonatales (6%) durante la primera semana de vida era comparativamente menor que en las semanas posteriores. Ello podría ser reflejo de la pérdida fisiológica de peso que típicamente sufren los recién nacidos en la primera semana de vida (alrededor del 10% del peso al nacer debido a pérdida de líquido corporal) siendo el aclaramiento del litio particularmente sensible a los cambios del volumen de fluidos (82).

Otra razón para desaconsejar la lactancia materna en mujeres en tratamiento con litio es la preocupación respecto a sus potenciales efectos adversos renales y tiroideos. Sin embargo, aunque los niveles de creatinina sérica neonatal son elevados durante los primeros días de vida no observamos nefrotoxicidad neonatal relacionada con el litio durante la lactancia. En los neonatos a término, los niveles de creatinina sérica son normalmente elevados al nacer debido a que se produce una trasferencia placentaria completa de creatinina. Esta creatininemia neonatal (0,70 mg/dl) es el reflejo de la función renal maternal y suele ir progresivamente disminuyendo lo largo de las siguientes semanas de vida que es cuando la creatininemia neonatal refleja la función renal propia del lactante (150). Sin embargo, la filtración renal glomerular estimada (mL/min/1.73m^2) del recién nacido es fisiológicamente baja en la primera semana de vida (5-40 ml/min/1.73 m^2) y continúa incrementándose (hasta los 65 ml/min/1.73 m2 a los dos meses de vida), llegando a alcanzar los niveles del adulto joven (120-130 ml/min/1.73 m2) a los 2 años de vida (151). En todos nuestros casos (N=9), la concentración de TSH neonatal se encontraba dentro del rango de normalidad a las 48 horas de vida. No se

realizaron determinaciones seriadas de TSH neonatal durante la lactancia materna debido a que la exposición del lactante a litio durante este período fue menor que durante el período fetal.

La naturaleza del sueño de las mujeres durante los primeros meses posparto se caracteriza por presentar un patrón de sueño fragmentado debido al amamantamiento y a las necesidades de cuidado del lactante (152). La lactancia materna exclusiva puede empeorar el patrón del sueño (en duración total y en fragmentación) (153). Es sabido que la alteración del patrón del sueño actúa como desencadenante de episodios maníacos en el trastorno bipolar, y que la posibilidad de presentar un episodio de psicosis puerperal es dos veces mayor (154) siendo los días 10-19 posparto el periodo de mayor riesgo para una descompensación psiquiátrica (45). Una revisión sistemática con metaanálisis mostró que la ratio de recaídas posparto era significativamente menor en mujeres en tratamiento profiláctico durante el embarazo que entre aquellas sin tratamiento. En nuestro caso, una mujer (11%) presentó a los 45 días postparto un episodio de manía con síntomas psicóticos a pesar de disponer de un plan prenatal para la minimización de la interrupción del sueño nocturno. Este porcentaje de descompensación posparto es menor que el descrito previamente en la literatura científica (45, 47).

En este estudio encontramos que el aclaramiento de litio en el lactante era independiente de la litemia maternal y que las concentraciones de litio en el lactante iban disminuyendo a lo largo del tiempo desde el parto a hasta el tercer mes de vida: un promedio de un 44 % en el primer mes de vida y un promedio de un 59% a los tres meses de vida. La litemia neonatal en la primera semana posparto reflejaba la transferencia placentaria más que la trasferencia a través de la leche materna (19).

Por último, hemos comparado el comportamiento farmacocinético del litio tras el parto en las tres trayectorias de lactancia posibles, materna exclusiva, mixta y artificial. El análisis de la trayectoria de la lactancia artificial (en el que la última exposición del recién nacido al litio es en el momento del parto) nos permite disponer de un punto de referencia con el que comparar el curso de las trayectorias de la lactancia materna

exclusiva y lactancia mixta en los primeros 7-10 días postparto. Aunque las concentraciones de litio disminuyen en las tres trayectorias, el tiempo necesario para alcanzar el límite de cuantificación de lítio (LoQ) es mayor en la trayectoria de lactancia materna exclusiva. La no acumulación de litio en el lactante puede explicarse por :1) la disminución del transporte de litio a la leche asociada a la edad del lactante; 2) por el incremento de la excreción renal neonatal del litio a medida que aumenta la maduración del sistema de transporte tubular renal con la edad, si bien tras el parto la maduración de la función tubular es más lenta que la maduración de la función glomerular (155).

Revisiones sistemáticas previas sobre el comportamiento farmacocinético del litio en el lactante no encontraron síntomas clínicos de intoxicación por litio en los lactantes con litemias inferiores a 0,30 mEq/L (105, 148, 156). Por este motivo, decidimos suspender la monitorización de las litemias en los lactantes una vez que las litemias llegaran a valores iguales o menores a 0,20 mEq/L en dos determinaciones analíticas consecutivas. (157). Elegimos el tiempo necesario para alcanzar el LoQ como variable dependiente debido a que las tres trayectorias de lactancia tenían diferentes tiempos de exposición al litio: en el grupo de lactancia artificial la última exposición fue en el momento del parto, mientras que en los grupos de lactancia mixta y materna exclusiva la exposición a litio continuó en diferentes proporciones. Sin embargo, los neonatos de las tres trayectorias de lactancia compartían los problemas de inmadurez del sistema renal y la pérdida fisiológica de fluidos corporales, que también pueden afectar a las concentraciones de litio.

En relación con los efectos de la exposición de litio transplacentaria en el momento del parto, en nuestra muestra seis neonatos presentaron complicaciones leves y transitorias que se resolvieron previo a recibir el alta hospitalaria. Durante el periodo de seguimiento pediátrico hasta el año de vida no se observaron retrasos del crecimiento o del desarrollo en ninguno de los lactantes de las tres trayectorias.

El periodo del postparto está asociado con un riesgo elevado de hospitalización de las mujeres con trastorno bipolar (45). El litio ha demostrado ser un tratamiento preventivo

eficaz durante el posparto (158). Una revisión sistemática con metaanálisis ha mostrado que el porcentaje de recaídas durante el posparto en las mujeres con trastorno bipolar es de un 37% (47). En el primer mes posparto, el rango terapéutico de litio recomendado es de 0,80-1,0 mEq/l (104). En nuestra muestra de mujeres con trastorno bipolar en tratamiento con litio en monoterapia durante la lactancia, solo dos de las 24 mujeres (menos del 10%) se descompensaron psiquiátricamente durante el seguimiento (a los 36 y a los 45 días posparto respectivamente): una mujer presentaba niveles séricos de litio subterapeúticos y la otra mujer niveles séricos de litio dentro del rango terapeútico.

9.1 Fortalezas y debilidades de esta investigación

Esta investigación observacional de cohortes retrospectiva tiene varias limitaciones relacionadas principalmente con su carácter retrospectivo y con la ausencia de un grupo control de mujeres embarazadas afectas de un trastorno bipolar sin tratamiento con litio que hubieran sido recogidas en el mismo periodo de tiempo. El diseño observacional puede haber introducidos sesgos de información. Las mujeres fueron tratadas de forma ambulatoria, por lo que no podemos asegurar que el intervalo de 12 horas entre la última toma de la dosis de litio y la obtención de la muestra de sangre para obtener los niveles de litio haya sido estrictamente observado. Ello puede haber incrementado la variabilidad de las medidas. Además, cierto grado de no adherencia puede haber ocurrido sin nuestro conocimiento, particularmente entre las mujeres con dosis múltiples (≥ 2). Por otra parte, en el 10% aproximadamente de las muestras analizadas, que corresponden a una dosificación única nocturna, se ha podido sobreestimar el valor de la litemia debido a que la recolección se ha realizado 12 horas posdosis. Las pacientes no embarazadas a las que se les prescribe litio en dosis única diaria tienen concentraciones de litio a las 12 horas que son entre un 10 y un 15% más altas que la concentración mínima. De acuerdo con las recomendaciones de Sociedad Internacional de Trastornos Bipolares (93), realizamos las mediciones de las concentraciones séricas de litio en estado estacionario (logrado después de tomar una dosis de litio constante durante al menos 5 días consecutivos) y en predosis de 12 ±2 horas después de la dosificación tanto en dosis única como en múltiple. La

información obtenida de la entrevista clínica es sabido que no es completamente informativa sobre el consume de fármacos durante el embarazo. Sin embargo, las pacientes con enfermedades crónicas (como es el caso del trastorno bipolar) realizan una mejor cumplimentación del tratamiento durante el embarazo que aquellas que presentan enfermedades agudas (como la hiperémesis). Por último, no se pudieron analizar en nuestro laboratorio las litemias preconcepcionales de todas las mujeres de nuestro estudio ya que más de un 50% de ellas no realizaron asesoramiento psiquiátrico preconcepcional en la Unidad de Psiquiatría Perinatal del hospital.

Además del potencial riesgo de complicaciones neonatales agudas tras exposición intraútero a litio, una importante preocupación entre los clínicos es la potencial teratogeneidad inducida por litio tras la exposición en el primer trimestre de gestación. Diversos trabajos de los años 70 del siglo pasado (131, 159) apuntan que la exposición de litio durante el primer trimestre se asocia a un incremento del riesgo de presentar una anomalía de Ebstein. En contraste, un metaanálisis realizado en 2012 (160) no confirmó un incremento de malformaciones congénitas cardiacas, incluida la anomalía de Ebstein. Sin embargo, los autores de este metaanálisis concluyeron que el riesgo teratogénico no se pudo excluir del todo debido a que la potencia de la mayoría de las muestras de los estudios no era suficiente para poder descartar un evento poco frecuente como este. Más recientemente, un estudio de cohorte retrospectivo de mujeres embarazas expuestas y no expuestas a litio durante el primer trimestre de gestación, ha estimado que la magnitud de este efecto es menor de lo que se había postulado previamente y es dosis dependiente (99), multiplicándose el riesgo por tres cuando se toman dosis diarias de litio por encima de los 900 mg/día. A todas las embarazadas expuestas a litio durante el primer trimestre de gestación se les practicó un ecocardiograma fetal precoz (semana 13-14) que se repitió en semana 16-18 de gestación para detectar anomalías cardiacas. Además, a todas ellas se les realizaron las evaluaciones médicas y exploraciones complementarias estandarizadas para las mujeres embarazadas de población general.

Dada la considerable morbilidad del trastorno bipolar no tratado y el riesgo elevado de recaída perinatal en ausencia de tratamiento psicofarmacológico continuado, la interrupción prolongada del tratamiento con litio, sobre todo alrededor del parto, rara

vez es una opción viable. Debido a que el litio tiene un estrecho margen terapéutico, la monitorización de la litemia en combinación con el seguimiento clínico está indicada para ajustar la dosis si es preciso, prevenir la recurrencia de los síntomas del trastorno bipolar y minimizar los efectos adversos en la diada madre-hijo. Comprender estos cambios y su profundo impacto en las propiedades farmacocinéticas del litio durante el parto es esencial para optimizar la salud materna y fetal/neonatal. Claramente, existe una necesidad urgente de estudios más extensos sobre los posibles efectos adversos del litio durante el embarazo, así como los resultados agudos y a largo plazo para los niños expuestos al litio en el útero. Estos estudios deben incluir a mujeres con trastorno bipolar no tratado como grupo de control, porque el trastorno bipolar en sí parece estar asociado con resultados adversos del embarazo (52).

Hasta donde llega nuestro conocimiento, hemos estudiado la muestra más extensa que investiga el comportamiento del litio en la diada madre-hijo alrededor del parto y los resultados neonatales agudos tras la exposición fetal a litio al final del embarazo. Fortalezas de este estudio son la homogeneidad de la muestra, el uso de una única formulación del litio, y que todas las litemias tanto de la madre como del neonato fueron extraídas simultáneamente y analizadas en el mismo laboratorio. Sin embargo, el estudio no está exento de debilidades. En primer lugar, el carácter retrospectivo de la cohorte y al tratarse de mujeres con embarazos sin factores de riesgo médico, hace que no se pueden generalizar los resultados a todas las mujeres en tratamiento con litio durante el embarazo. Al tratarse de un estudio naturalístico, de práctica clínica real, no se pudo recoger muestra analítica materna en todos los tiempos de extracción del periparto. Nuestro estudio no disponía de un grupo control de mujeres con embarazos no complicados, sin tratamiento con litio, recogidas en el mismo periodo de tiempo. Finalmente, el tamaño de la muestra fue moderado dado que no disponíamos de más mujeres embarazadas expuestas a tratamiento con litio desde que iniciamos tratamiento estandarizado (161).

El estudio de la serie de nueve diadas madre-hijo en lactancia maternal exclusiva tiene varias limitaciones. La primera es que se trata de un estudio limitado tanto en el tamaño de la muestra como en la duración. Sin embargo, la FDA en su guía de 2005 (17) para estudios clínicos de lactancia de la industria farmacéutica considera que la muestra

necesaria para los diseños madre-hijo es de 6-8 casos. La segunda es que se trata de una serie de casos de mujeres con trastorno bipolar clínicamente estables y en tratamiento en monoterapia con litio durante al menos el tercer trimestre de gestación y el periodo de lactancia exclusiva y neonatos sanos. Aunque los hallazgos no pueden ser generalizados a cualquier mujer con trastorno bipolar tratada con litio, los resultados contribuyen a acumular evidencia ayudando a los clínicos y a las pacientes a la hora de tomar decisiones compartidas acerca del mantenimiento de litio durante la lactancia. Tercera, no utilizamos una exploración estandarizada para evaluar a los recién nacidos durante el seguimiento. Finalmente, somos conscientes de los límites de detectabilidad de los ensayos utilizados para determinar las litemias neonatales esencialmente en aquellos casos por debajo del límite de cuantificación (0,20 mEq/L).

Por último, las fortalezas del estudio es la posibilidad de haber evaluado las tres trayectorias de lactancia posibles desde el momento del parto en tres grupos cada uno de ocho mujeres con características sociodemográficas y obstétricas semejantes. En cuanto a las limitaciones, el estudio fue realizado en unas muestras de mujeres con trastorno bipolar estables y en tratamiento con litio en monoterapia durante el embarazo y sus correspondientes recién nacidos sanos y a término. Por lo que nuestros resultados no pueden generalizarse a mujeres de poblaciones más heterogéneas (tratadas con litio en politerapia, recién nacidos prematuros o enfermos…). La cantidad de litio transferida a los lactantes pudo ser medida directamente en el suero del neonato. La concentración sérica de litio en el lactante proporciona información sobre la cantidad de fármaco que está sistemáticamente disponible en el lactante (15). Es la medida más directa para la evaluación de riesgos en el lactante (17,18), motivo por el que decidimos utilizar esta medida. Sin embargo, el tener que obtener una muestra de sangre en el recién nacido puede ser una limitación al tratarse de un método invasivo que puede producir dolor y puede ser rechazado por los padres. Debido a ello, algunos autores han propuesto la determinación de la litemia en saliva, pero desde un punto de vista preanalítico, obtener saliva en recién nacidos menores de 2 meses no es algo sencillo y, por otro lado, el rango terapéutico del litio en esta matriz no ha sido definido (162). Por otro lado, somos conscientes del límite de detectabilidad del ensayo utilizado para medir la concentración sérica de litio, especialmente en aquellos valores por debajo del límite de cuantificación (LoQ).

9.2 Líneas de futuro de esta investigación

El embarazo está asociado con cambios fisiológicos que pueden alterar la farmacocinética y la farmacodinámica de los fármacos en general y de los psicofármacos en particular. Hay información limitada disponible sobre la farmacocinética (FC) y la farmacodinámica (FD)a de los psicofármacos en el periodo perinatal, en parte a los problemas medicolegales y en parte a las dificultades prácticas de realizar estudios en esta subpoblación.

Desafortunadamente, la falta de estudios de FC y PD específicos del embarazo debido a una brecha entre la licencia inicial de un medicamento y la disponibilidad de datos farmacológicos específicos del embarazo ha provocado retrasos en la implementación y el uso de fármacos en mujeres embarazadas. Como resultado, muchos fármacos eficaces que se prescriben ampliamente a adultas no embarazadas no se utilizan actualmente en mujeres embarazadas. Comprender la fisiología del embarazo es importante para la investigación farmacológica porque nos permite responder preguntas cruciales sobre los efectos de los fármacos en mujeres embarazadas y cómo el embarazo modifica la PC y la PD de los fármacos y proporciona los datos fisiológicos necesarios para una mejor comprensión del modelado PK con base fisiológica, con el objetivo de acelerar los estudios farmacológicos de búsqueda de dosis y respuesta a la dosis en mujeres embarazadas

El futuro de la investigación en psicofarmacología reproductiva pasa por incorporar estos modelos farmacocinéticos que permiten relacionar la cantidad de exposición a fármacos con la cantidad de fármaco presente en la sangre y en los órganos (p.ej. tejido fetal/órganos del neonato) en diferentes períodos del embarazo y el posparto/lactancia. la (79).

10 CONCLUSIONES

1. La monitorización de las concentraciones séricas de litio son esenciales antes, y durante el embarazo, así como en el posparto para asegurar una dosificación del litio adecuada.

2. Se recomienda evaluar las concentraciones séricas de creatinina como medida de monitorización del aclaramiento renal del litio.

3. Tras los resultados obtenidos en el estudio se sugiere realizar una monitorización cuidadosa de la litemia hasta la semana 30 de embarazo, para pasar a litemia semanal hasta el parto y (bi-)semanal durante el primer mes posparto.

4. Esta investigación ratifica estudios previos de la literatura realizados en muestras pequeñas y poco homogéneas, de que la transferencia placentaria del litio es completa para un amplio rango de concentraciones séricas de litio y un amplio rango de semanas de gestación.

5. Una discontinuación breve del tratamiento con litio antes del parto se asocia pequeñas fluctuaciones de la litemia maternal que unido a un reinicio del tratamiento al cabo de 6-12h del parto no comprometen el efecto preventivo del tratamiento con litio.

6. En lactantes de madres tratadas con litio durante el embarazo no se observan acumulación de litio, a pesar de que el tiempo para alcanzar el límite de cuantificación de litio con nuestra técnica fue superior en la trayectoria de lactancia maternal exclusiva.

7. Los lactantes de madres tratadas con litio, independientemente del tipo de trayectoria de lactancia elegido, no mostraron alteraciones el desarrollo tanto a corto plazo como al año de evolución.

8. En mujeres con trastorno bipolar, el tratamiento con litio durante la lactancia materna exclusiva no es una contraindicación si va asociada a una cuidadosa monitorización clínica y analítica de la diada madre-hijo.

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