DEATH AND SEVERE MORBIDITY IN ISOLATED PERIVIABLE SMALL-FOR-GESTATIONAL-AGE FETUSES: a Research article

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Running Title: Periviable SGA: prediction of severe sequelae

ABSTRACT

Objective: This study aims to predict perinatal death or severe sequelae in isolated small-for-gestational-age fetuses diagnosed at a periviable gestational age based on ultrasound and Doppler parameters at diagnosis.

Design: Observational study

Setting: A a tertiary perinatal center.

Population: A cohort of singleton non-malformed fetuses suspected of small-for-gestational-age (estimated fetal weight<10^{th} centile) diagnosed at 22-25.6 weeks. The following parameters were recorded at diagnosis: severe smallness (<3rd centile), absent and reversed end-diastolic velocity in umbilical artery, abnormal middle cerebral artery Doppler, abnormal cerebroplacental ratio, abnormal uterine artery Doppler, and absent or reversed end-diastolic velocity in the ductus venosus.

Methods: Logistic regression analysis

Main Outcome Measures: Predictive performance of EFW and Doppler parameters for short-term adverse outcome of perinatal morbimortality and composite serious adverse outcomes (death, neurologic impairment, or severe bronchopulmonary dysplasia).

Results: 155 pregnancies were included. There were 13 (8.4%) intrauterine and 11 (7.7%) neonatal deaths. A short-term adverse perinatal outcome occurred in 40 (25.8%) pregnancies. There were 31 (20%) cases of serious adverse outcomes. For the prediction of serious adverse outcomes, the combination of absent and reversed end-diastolic velocity in the umbilical artery and impaired middle cerebral artery detected by Doppler evaluation achieved a DR of 87% for a FPR of 14% [accuracy 86%].

Conclusion: In periviable-isolated small-for-gestational-age fetuses, a Doppler evaluation of the umbilical and fetal brain circulation can accurately predict short-term adverse perinatal complications and serious adverse outcomes.

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Keywords: Small-for-gestational-age; Placental insufficiency; Fetal growth restriction; Perinatal mortality; Neonatal complications; Neurologic impairment

TWEETABLE ABSTRACT

Umbilical and fetal brain circulation can accurately predict serious adverse outcomes among periviable-isolated SGA fetuses.

INTRODUCTION

A fetus is considered SGA when its size (biometric evaluation) falls below a predefined threshold for its gestational age (usually, the 10th centile). Not interchangeably, fetal growth restriction (FGR) reflects a failure of the fetus to reach its growth potential. Both conditions are more relevant when diagnosed early in the pregnancy. Genetic abnormalities may be present in up to 20% of SGA fetuses detected early in pregnancy[1], and chromosomal microarray analysis could be offered when there is suspicion of genetic syndrome[2]. When a genetic cause has been excluded, dating is accurately performed and no signs of intrauterine infection are observed, placental dysfunction is the most plausible condition in 80% of the cases[3]. In placenta-related early-onset growth-restricted fetuses, risks of perinatal mortality and neonatal morbidity are much higher than in late FGR[4].

Currently, placental FGR is not a treatable condition[5] and is designated by the European Medicines Agency as an orphan disease[6]. Extensive research for improving poor placentation and/or uterine blood flow is providing encouraging results[7,8]. Intensive management with timely delivery under antenatal neuroprotection and fetal lung maturity remains the standard of care to date[9].

It is well documented that extremely preterm SGA fetuses have a worse prognosis at birth and long term than normal fetuses[10]. It has been proposed to move common thresholds for intervention at extremely low gestational ages in preterm babies (22-25 weeks) to 26-28 weeks when FGR is present, as this threshold identifies fetuses with significantly better survival rates without severe morbidity[11,12]. Identification at the time of diagnosis of FGR fetuses that will die in utero or have severe sequelae is crucial for parental counseling and shared decision-making.

An expert consensus has been published on the definition of early and late FGR according to the gestational age at diagnosis [Delphi consensus][13]. Moreover, a stage-based classification based on Doppler parameters and the severity of smallness[9] has been proposed for better optimization of the follow-up and timing of

delivery to minimize the risk of intrauterine death. However, none of these classifications has been designed for predictive assessment of mid- and long-term neonatal outcomes at the time of diagnosis of periviable SGA.

This study aimed to predict intrauterine or perinatal death and severe sequelae in isolated SGA fetuses diagnosed at periviable gestational ages based on findings of placental insufficiency at diagnosis.

METHODS

Subjects

A cohort was collected of consecutive patients referred between January 2010 and January 2020 to a single center [Barcelona Center for Maternal-Fetal and Neonatal Medicine]. The inclusion criteria for this study were as follows: (i) singleton pregnancy, (ii) an estimated fetal weight (EFW) of less than the 10th centile according to local reference values[14], and (iii) diagnosis between 22.0 and 25.6 weeks (according to first-trimester crown-rump length[15]). Exclusion criteria were severe/major congenital anomalies, genetic abnormalities with clinical significance, and congenital infections. In consequence, we have defined them as isolated SGA. Because the aim of the study was to define predictive tools for counseling women with previable SGA, conditions that were not diagnosed in the initial workup study were not excluded.

The study was approved by the local ethics committee, and all women gave their informed consent to participate (IRB/2008/7315). The study design, analysis, and reporting adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations[16].

Measurements

In all study cases, experienced fetal medicine specialists performed an accurate anatomical examination, fetal biometry, and prenatal Doppler ultrasound examinations at the time of diagnosis. The estimated fetal weight (EFW) was calculated from the biparietal diameter, head and abdominal circumferences, and femur length using the Hadlock formula[17]. Doppler measurements of the umbilical artery (UA), middle cerebral artery (MCA), uterine artery (UtA), and ductus venosus (DV) were performed according to standardized recommendations[18]. The cerebroplacental ratio (CPR) was calculated as the ratio of MCA to UA pulsatility index (PI).

In those cases with an EFW below the 3rd centile before 24 weeks of gestation, microcephaly (<-3 SD), and/or short femur length (<-3 SD), invasive testing was offered for a karyotype or chromosomal microarray analysis. In addition, unless there was serological evidence of negative immunoglobulin G (IgG) and immunoglobulin M (IgM), a study of cytomegalovirus infection by amniotic fluid PCR was performed.

All pregnancies were classified as FGR if any of the following criteria were met[19]: EFW below the 3rd centile[13], abnormal UA (≥95th centile[20]), or abnormal UtA PI (≥95th centile[21]). When none of the criteria were met, pregnancies were considered SGA. Follow-up was performed every 2 weeks in cases without criteria for FGR, and at least weekly in those meeting these criteria.

Preeclampsia and severe preeclampsia were defined according to the ISSHP criteria[22].

Patients were not involved in the research project.

Management

Umbilical and cerebral Doppler evaluations were performed on each visit. Uterine Doppler evaluation was performed at diagnosis and, when the evaluation was found to be normal, re-evaluated every 4 weeks. Ductus venosus Doppler evaluation was done at diagnosis and afterward only when Doppler signs of placental insufficiency/hypoxia were present (abnormal uterine, umbilical, or cerebral Doppler). Conventional cardiotocography was done after 26 weeks of pregnancy in those pregnancies with placental insufficiency/hypoxia (abnormal CTG is defined as reduced/absent fetal heart rate variability, recurrent decelerations, or persistent bradycardia).

Before 30^{+0} weeks, only abnormal CTG and absent or reversed end-diastolic velocity (EDV) in the DV were fetal indications for delivery (cesarean section). After 30^{+0} weeks, reversed EDV in the UA or a DV pulsatility index of >95th centile were additional indications for delivery (cesarean section). Absent EDV in the UA was an additional indication for delivery after 34^{+0} weeks (cesarean section). Induction of labor was

recommended at 37^{+} weeks in cases with UtA of >95^{th} centile or CPR of <5^{th} centile or EFW of <3^{rd} centile. In the remaining pregnancies, induction was recommended at 40^{+} weeks of pregnancy.

Magnesium sulfate for neuroprotection and steroids for pulmonary maturation were administered as soon as the termination of pregnancy was decided at 34^{+0} and 35^{+0} weeks of gestation, respectively.

Outcome definitions

- A short-term adverse outcome of perinatal morbidity or mortalityas defined by any of the following: intrauterine death; neonatal death (<28 days); neonatal sepsis (systemic inflammatory response syndrome with a central positive culture); abnormal cranial ultrasound (cystic periventricular leukomalacia and/or intraventricular hemorrhage > grade II); hypoxic-ischemic encephalopathy; necrotizing enterocolitis (requiring surgery); acute renal failure (serum creatinine >1.5 mg/dL); cardiac failure (requiring ionotropic agents); respiratory distress syndrome (clinical signs of breathing difficulties, such as grunting sounds, rapid, shallow breathing, sharp pulling inward of the muscles between the ribs when breathing, widening of the nostrils, or flaring, with each breath, and X-ray signs of atelectasis or lung collapse);

- A composite serious adverse outcome as defined by as mortality or severe morbidity:

  1) Mortality was defined as intrauterine death [including feticide/termination of pregnancy (TOP)], neonatal death, or infant death during the follow-up.

  2) Severe morbidity was defined as cognitive impairment below 85 [Bayley Scales of Infant and Toddler Development third edition (Bayley-III)]; cerebral palsy[23]; hearing loss (evaluated by evoked otoacoustic emissions at <2 years of age, play audiometry at 2-4 years of age, or conventional audiometry at >4 years of age; visual loss [6 months to 2 years of age: failure to

fix and follow; 3-4 years of age: visual acuity <0.4; 4-5 years of age: visual acuity <0.5; and ≥5 years of age: visual acuity <0.66][24]; or severe bronchopulmonary dysplasia (need for ≥30% oxygen and/or positive pressure at 36 weeks postmenstrual age or discharge, whatever comes first)[25].

Statistical analysis

The student-t-test for independent samples and Chi-squared test (or Fisher exact test) were performed to compare variables between groups. The univariate association of each parameter with the main and secondary outcomes was assessed by calculating the adjusted odds ratios from a logistic regression model. The multivariable association of the clinical predictors with the main and secondary outcomes was evaluated by logistic regression and backward selection of variables (inclusion and exclusion probability criteria for the admission and exclusion of variables were 0.05 and 0.1, respectively). As a background comparison, the predictive performance of the Delphi consensus[13] for FGR and that of the stage-based classification proposed by our group, both at the time of inclusion[9], were also calculated by logistic regression. The predictive capacity of each model was evaluated with receiver operating characteristic (ROC) curve analysis of the predicted probabilities. Confidence intervals of the performance parameters were obtained by bootstrapping (2000 replicates). Optimal cut-offs were identified by the Youden method (maximizing the sum of Sensitivity and Specificity). Paired ROC curves were compared by the De Long method[26].

The statistical packages IBM SPSS 23.0 (New York, USA) and R v3.1.2 (The R Foundation for Statistical Computing) [package "pROC"] were used to conduct all the statistical analyses.

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RESULTS

Of the 161 cases recruited, 99 women were offered invasive genetic testing and six declined, 44 had a chromosomal microarray analysis, and 49 had a conventional karyotype procedure. Fifty-one women were tested for cytomegalovirus (CMV) by polymerase chain reaction (PCR) in amniotic fluid because of the presence of maternal serologies other than negative IgG and IgM antibodies. For the final analysis, six cases were excluded; two cases because of a severe major malformation (one case of lissencephaly and one case of esophageal atresia), and four cases because of prenatal genetic abnormalities (47 XXY, trisomy 21, micro-duplication of 3p26.3, and micro-deletion 12p of 5q15) with clinical implications.

Among the remaining 155 cases, one case with a genetic anomaly without known clinical significance [46, XX inv (8) (p11.2q13)] was included. Seven additional cases had isolated minor abnormalities with normal microarray analysis (two with ventricular muscular septum defects of <2 mm, one with bilateral club feet, one with hypospadias, one with a webbed penis, one with a horseshoe kidney, and one with an incomplete cleft lip).

During the antenatal follow-up, 25 women (16.1%) developed preeclampsia. 23 out of the 25 cases with PE occurred in cases meeting Delphi criteria for FGR

There were 13/155 (8.4%) intrauterine deaths, including one termination of pregnancy for severe FGR in a woman with severe preeclampsia. Among the 142 live births, there were 11 neonatal deaths (7.7%). A short-term adverse perinatal outcome occurred in 40 (25.8%) pregnancies. Infants were followed up for an average of 69 months (IQR 46.2, range [9.4-122]). There were 31 (20%) cases with serious adverse outcomes. In one of them, a postnatal diagnosis of a linear nevus sebaceous syndrome was made. No other congenital malformations or genetic syndromes were found postnatally.

231 The baseline characteristics and the ultrasound and Doppler findings at diagnosis are shown in Table 1, and
232 the perinatal outcomes are shown in Table 2. The Doppler characteristics at diagnosis and the univariate
233 association of each parameter to the adverse outcomes are shown in Table S1 and Figure S1, respectively.

234 Multivariable analysis of the adverse outcomes is shown in Table S2. It is noteworthy that both for short-
235 term adverse perinatal outcome and serious adverse outcome, only the UA and MCA Doppler results
236 retained an independent and significant association. We further explored (in a post hoc analysis) whether
237 there would be an effect on MCA PI as a predictor using different comparisons of UAPI. Hence, we re-run
238 the regression using UAPI>95th vs <95th centile, instead of <95th centile vs. >95th centile with +DV and
239 AREDV. The MCA remained as a significant independent predictor.

240

241 The prediction capacity of the model combining the UA ($\leq 95^{th}$ centile, $>95^{th}$ centile with positive diastolic
242 flow and AREDV) and the MCA ($<p5^{th}$ vs. $\geq 5^{th}$ centile) Doppler results was significantly better than the model
243 including only the UA, both for short-term adverse perinatal outcome (AUC 0.82 vs. 0.75; p=0.018) and
244 serious adverse outcome (AUC 0.89 vs. 0.79; p=0.01). The predicting performance for fixed false-positive
245 rates is shown in Table 3.

246 The ROC curves and predictive performance of the optimal cut-off are shown in Figures 1a and 1b.
247 Regarding the prediction of short-term adverse perinatal outcome, the combination of umbilical and MCA
248 Doppler results achieved a detection rate (DR) of 73% for a 14% FP [accuracy 83%] (+LHR 5.21 [3.18-8.53];
249 -LHR 0.32 [0.19-0.53]). For the prediction of serious adverse outcome, the same combination of parameters
250 achieved a DR of 87% for a 14% FP [accuracy 86%] (+LHR 6 [3.83-9.39]; -LHR 0.15 [0.06-0.38]).

251 Figure S2 and Figure S3 show the predictive performances of the model combining the UA and MCA
252 Doppler results of the stage-based FGR classification and of the Delphi consensus for FGR. Of note, the

AUCs [95% CI] of the model combining AU and MCA were higher for short-term adverse perinatal outcome (0.82 [0.73-0.91], 0.79 [0.72-0.87], 0.61 [0.56-0.67], respectively) and for serious adverse outcome ([0.89 (0.81-0.96), 0.85 [95% CI 0.78-0.91], 0.63 [95% CI 0.58-0.68], respectively).

DISCUSSION

Main findings

Following the diagnosis of SGA at a periviable gestational age, parents' concerns focus on short-term adverse outcomes, especially intrauterine/neonatal death, and long-term severe morbidity outcomes like neurological impairment. Therefore, parental counseling is needed for decision-making options (e.g., expectant management, planned delivery, termination of pregnancy). . In periviable SGA fetuses without known congenital and genetic abnormalities, the prediction of serious adverse outcomes could be achieved at an accuracy of 86% by combining UA and MCA Doppler results.

Comparison with previous studies

In our study, 4 of 5 pregnancies with periviable SGA without major fetal structural or genetic abnormalities had intact survival outcomes (live infant without severe sequelae). Monier et al.[12] evaluated the impact of gestational age at diagnosis on rates of live birth and survival to discharge of 436 SGA fetuses diagnosed before 28 weeks; 67% were live born and 42.8% survived to discharge without severe morbidity. These poorer outcomes are probably due to placental dysfunction severity as 61% had fetal Doppler findings, suggesting selection bias towards more severely affected babies. A retrospective study[27] comprising 122 SGA babies diagnosed at 21.1 (SD 3.6) weeks found that 80.3% resulted in a live birth after 34 weeks of gestation. Dall'Asta[28] evaluated outcomes of 136 non-anomalous SGA fetuses diagnosed at 22-26 weeks, after structural or genetic anomalies were excluded. Like our results, 90% of all non-anomalous SGA fetuses survived into infancy, but a high mortality rate (93%) was found among those born before 28 weeks.

Few studies assessed long-term neurological morbidity in very early SGA/FGR. A recent systematic review[29] of seven series of SGA fetuses (diagnosed before 32 weeks) reported cognitive impairment and/or cerebral palsy in 12% of surviving children. Only one series[30], comprising fetal growth restricted fetuses, included all relevant domains in the definition of neurodevelopmental impairment (Bayley III score, cerebral palsy,

hearing or visual loss). Ten percent of surviving children were affected at follow-up, and all fetuses had signs of placental insufficiency. These results represent a homogeneous group of FGR babies diagnosed at 26-32 weeks. This evidence would be difficult to translate into the clinical scenario of diagnosis before 26 weeks, when SGA-diagnosed babies present a higher phenotypic variability, including placental, genetic an infectious and constitutional causes.

Clinical implications

Consensus exists to differentiate early (<32 weeks) and late FGR according to gestational age at diagnosis [Delphi consensus[13], ISUOG guidelines 2020[19]]. Early-onset cases have a high degree of placental involvement as reflected by the large proportion of abnormal umbilical artery Doppler results and strong association with preeclampsia (up to 50% [11]); therefore, the prognosis is a priori poorer in terms of fetal and perinatal outcomes. However, SGA fetuses detected at a periviable gestational age correspond to a more heterogeneous group than placental-FGR cases. After major malformations were ruled out, 10% of cases with genetic abnormalities remained. One clinical implication of this is genetic testing should be strongly recommended for decision-making. We and others reported that genetic array has a 10% incremental yield over conventional karyotypes in this group of babies[31]. Of the remaining non-genetic and non-anomalous fetuses, placental insufficiency as reflected by abnormal UA or UtA artery Doppler accounts for half the cases. The heterogeneous composition of the periviable SGA fetuses group is further supported by our finding that only 15% developed pre-eclampsia during follow-up.

We found that the predictive capacity for serious adverse neonatal outcomes with our model based on UA and MCA at very early diagnosis is more accurate than the stage-based protocol model and Delphi classification for growth restricted fetuses While the latter models are not primarily intended to predict adverse outcome but to guide the follow-up and delivery of small fetuses through the third trimester, our

model aims to assess the risk of death and serious adverse outcomes based on initial findings at diagnosis of periviable small fetuses.

Pathophysiology of findings

One novel finding is abnormal brain Doppler (MCA PI<5th centile) at diagnosis of periviable SGA adds predictive value to UA Doppler for adverse outcomes predictions. The Delphi consensus[13] of the early-onset FGR definition did not include MCA Doppler because 25% of experts considered this parameter relevant for the distinction of FGR from constitutional smallness. In our series, abnormal MCA at diagnosis conferred a 9-fold increase in the likelihood of death or long-term sequelae. This association may be due to the role of MCA as a surrogate of brain hypoxia. In a seminal study, Akalin-Sel et al.[32] performed fetal blood sampling in 32 severe FGR fetuses and found an association between low pulsatility indices in MCA, low levels of pO_2, and reduced pH values in umbilical cord blood. Few clinical studies have reported the additive contribution of MCA to UA Doppler in predicting abnormal neurological outcome in early FGR[33,34]. However, contrary to our series, they considered MCA assessment before delivery and not at diagnosis. These studies included FGR fetuses delivered before 34 weeks, not only those diagnosed at a very early gestational age. Likewise, a study including 941 SGA babies showed superior performance of the CPR over the UA in predicting stillbirth (occurring before 34 weeks).[35] Our finding of MCA Doppler adding predictive capacity cannot be explained by a treatment paradox bias, because decision-making in early FGR was not influenced by this parameter. Until 30 weeks of pregnancy, the only Doppler parameter that guided our clinical management was abnormal DV flow, which reflects diastolic failure secondary to fetal acidemia[36]. We found abnormal DV at diagnosis of periviable SGA was associated with a 12-fold increase in odds of death or sequelae. Padilla-Gomes et al.[33] compared severely affected FGR neonates delivered before 32 weeks of gestation due to absent or reversed atrial flow in the DV, with premature newborns matched by gestational age

without FGR. FGR neonates had a significantly higher prevalence of periventricular echogenicity or leukomalacia, intraventricular hemorrhage, and neonatal mortality. In our series, DV PI>95th centile was not independent of other Doppler parameters and did not remain significant at multivariate analysis. Twelve of 13 fetuses with absent or reversed end-diastolic velocities in the DV also had this pattern in the UA. Similarly, in a large cohort of early-onset FGR babies, Baschat et al.[36] did not find a predictive value of DV for neonatal death or sequelae in babies delivered before 29 weeks.

Strengths and limitations

Most published series on very early FGR include only babies delivered below a given gestational age. However, they do not represent the full spectrum of babies diagnosed with such condition. At the time of initial parental counseling in periviable pregnancies affected with FGR, the gestational age at which the baby will be delivered is unknown and therefore it is likely to be counterfactual when based on results from preterm series. Besides, most studies evaluating the predictive value of Doppler parameters for adverse outcome in these babies consider the measurements before delivery, which are neither available at the time of initial diagnosis. By including all diagnosed cases of periviable FGR and by considering the baseline Doppler parameters, our study provides valuable information for parent-counseling. We also acknowledge some limitations. First, the sample size renders the study underpowered to analyze individual outcomes rather than composite ones. Similarly, the low prevalence of some abnormal parameters may have prevented their inclusion in the predictive model. Second, the study data were collected in a real setting of routine health care, and therefore we cannot exclude that the knowledge by the managing clinicians of the study variables (such as the Doppler parameters) may have influenced the perinatal outcomes. However, our institutional practice adheres to well-established protocols and it is regularly audited, with little clinical variability. The Doppler parameters we found at the initial assessment for the prediction of adverse outcome (UA and MCA) are not triggers for delivery before 30 weeks in our clinical practice, and

348 therefore a treatment paradox seems unlikely to have influenced our findings. However, we cannot
349 completely rule out this bias, since the follow-up regime may have been influenced by the baseline findings.
350 Third, the follow-up has been done before 2 years of life in some of the children, which may have limited
351 our capacity to reliably assess the outcome. We admit that a control group of non-restricted preterm
352 babies would have been informative in distinguishing the effects of prematurity and growth restriction.
353 Finally, our cohort of periviable small-for-gestational-age fetuses is only representative of the cases
354 attended in a specialized unit and therefore caution is needed before translating our findings to other
355 settings where referral to these units is not a common practice.

356 Conclusion

357 An overall assessment at diagnosis of periviable SGA is necessary for parental counseling about short- term
358 and severe outcomes. After congenital malformations and genetic abnormalities are ruled out, Doppler
359 evaluation of umbilical and fetal brain circulation can accurately predict adverse perinatal complications
360 and serious adverse outcomes, like death, impaired neurocognitive development, or severe
361 bronchopulmonary dysplasia.

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Disclosure of interest

No conflicts of interest to be declared.

Contribution to authorship

All authors accept responsibility for the paper and all of them meet all the criteria set out in the journal's authorship criteria. Below, find itemized each author's contribution:

Eva Meler and Francesc Figueras have been main responsibles for the conception and the planning of this research paper.

Eva Meler, Edurne Mazarico, Anna Peguero, Killian Vellvé and Francesc Figueras have been in charge of the follow-up and management of the cases.

Alba Gonzalez , Judit Martinez and David Boada have contributed database management and analyzes.

Gemma Arca has contributed in the assessment and identification of the severe outcomes.

Eva Meler and Francesc Figueras have analyzed the data.

Eva Meler and Francesc Figueras have jointly written up the manuscript draft to be approved by all the authors.

Maria Dolores Gómez-Roig, Eduard Gratacós and Francesc Figueras have assessed the writing up of the manuscript.

All the authors have approved the final version of the manuscript to be published

Details of Ethics Approval

This research project has been developed according the Declaration of Helsinki and according the European Regulation (UE) 2016/679 from the European Parliament and the Counsel, of the 27th of April 2016 in relation to the protection of individuals with regard to the processing of personal data and the free movement if such data and Organic Law 3/2018, of 5th December, on the protection of personal data and

the guarantee of digital rights. The project was reviewed and approved by the local Ethics committee (IRB/2008/7315).

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