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Cervical consistency index and quantitative cervical texture analysis by ultrasound to predict spontaneous preterm birth

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Quantitative Analysis of the Cervical Texture by Ultrasound and Correlation with Gestational Age

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Key Words

Quantitative ultrasound · Uterine cervix · Image biomarker

Abstract

Objectives: Quantitative texture analysis has been proposed to extract robust features from the ultrasound image to detect subtle changes in the textures of the images. The aim of this study was to evaluate the feasibility of quantitative cervical texture analysis to assess cervical tissue changes throughout pregnancy. ***Methods:*** This was a cross-sectional study including singleton pregnancies between 20.0 and 41.6 weeks of gestation from women who delivered at term. Cervical length was measured, and a selected region of interest in the cervix was delineated. A model to predict gestational age based on features extracted from cervical images was developed following three steps: data splitting, feature transformation, and regression model computation. ***Results:*** Seven hundred images, 30 per gestational week, were included for analysis. There was a strong correlation between the gestational age at which the images were obtained and the estimated gestational age by quantitative analysis of the cervical texture (R = 0.88). ***Discussion:*** This study provides evidence that quantitative analysis of cervical texture can extract features from cervical ultrasound images which correlate with gestational age. Further research is needed to evaluate its applicability as a biomarker of the risk of spontaneous preterm birth, as well as its role in cervical assessment in other clinical situations in which cervical evaluation might be relevant.

Introduction

Cervical ripening is a chronic process, consisting in microstructural and water concentration changes, which starts during the first trimester and progressively proceeds until term in a normal pregnancy. Four differentiated phases have been described: softening, ripening, dilation, and repair. Initially, there is a progressive softening of the cervix beginning early in pregnancy, due to a reorganization of the collagen fibrillar network. There is also an increase in the vascularity and oedema of the entire cervix, a hypertrophy of cervical stroma, and hypertrophy and hyperplasia of the cervical glands. Shortening

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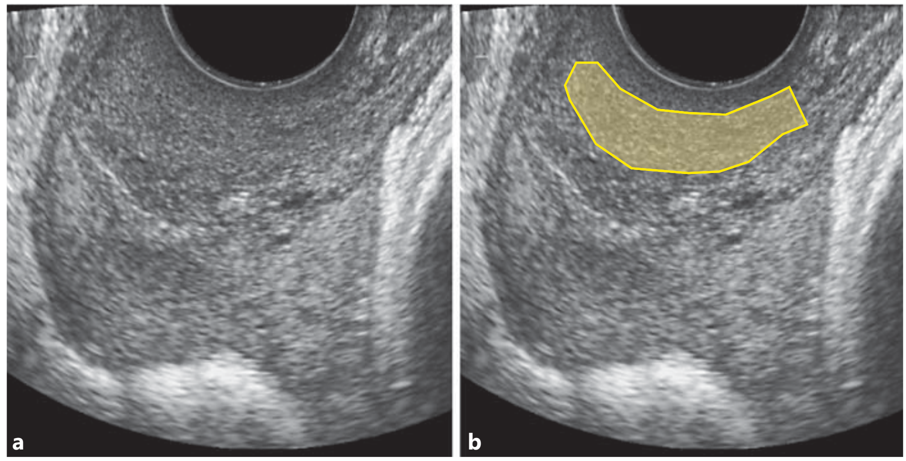

Fig. 1. Sagittal view of the cervix (**a**) and delineation of the anterior cervical lip (**b**).

and dilatation occur as later events, several days before delivery [1, 2]. Nonetheless, these major alterations in the extracellular matrix and cellular composition of cervical tissue taking place during pregnancy are subtle and difficult to detect by a clinical or routine sonographic examination.

Appropriate timing in cervical function and composition during gestation are crucial for a successful pregnancy. Premature cervical remodelling and ripening usually precede a spontaneous preterm birth regardless of the initial etiology [3], and an unripe cervix will probably lead to a failed induction of labor (IOL) [4]. With the lack of good tools to assess cervical remodelling [5], there is growing scientific interest to learn more about cervical structure and behaviour.

Several studies have suggested that women with a short cervix (≤20 mm) in the mid-trimester of pregnancy are at increased risk of spontaneous preterm birth [6]. Nevertheless, the prevalence of a short cervical length and its sensibility for the detection of spontaneous preterm birth are extremely low [7–9]. Consequently, only a small proportion of pregnant women are identified as being at high risk of preterm delivery and potentially benefit from the treatments available [10–12]. For these reasons, the value of the cervical length as a universal screening tool remains controversial. Therefore, other objective methods or strategies aimed at detecting early stages of cervical remodelling in order to better identify women at high risk are needed.

Quantitative texture analysis by ultrasound has demonstrated to extract robust features related to subtle differences in the textures of ultrasound images. Texture analysis by ultrasound or magnetic resonance has also been investigated in the field of foetal and perinatal medicine [13, 14]. Recently, quantitative texture analysis of foetal lung ultrasound images has proven to be a predictor of neonatal respiratory morbidity [15–17]. The aim of this study was to evaluate the feasibility of quantitative analysis of cervical ultrasound images to evaluate cervical tissue changes throughout pregnancy.

Methods

This was a cross-sectional study including women with singleton pregnancies between 20.0 and 41.6 weeks of gestation attending the Barcelona Center for Maternal Fetal and Neonatal Medicine in Hospital Clínic and Hospital Sant Joan de Déu in Barcelona for routine pregnancy ultrasound scans from March 2014 to January 2015. Multiple pregnancies, patients who received any treatment to prevent spontaneous preterm birth (progesterone or cervical cerclage), and women who delivered at <37 weeks were excluded from the study. Demographic characteristics, obstetrical history, gestational age at delivery, and mode of delivery were collected. The study protocol was approved by the local Ethics Committee (ID HCB 2014/0089), and all pregnant women provided written informed consent. Gestational age was calculated based on the crown-rump length at first-trimester ultrasound.

Image Acquisition and Region of Interest

An image acquisition guide was designed in order to ensure the optimal acquisition parameters for further analysis of the images: a sagittal view of the cervix without exerting any pressure with the transducer, so that the diameter of the anterior and posterior cervical lips were similar, was obtained. The internal and external os, as well as the cervical canal, should be identified and the entire cervical structure visualized, avoiding zoom and using only depth function. The cervix should be located horizontally to the transducer. Calipers, shadows, and saturations must also be avoided. Images had to be obtained without any post-processing function, such as speckle reduction imaging, smoothing, and on-line measurements, as shown in figure 1a. Gain and harmonics were at the discretion of the physician. Siemens Sonoline Antares (Siemens Medical Systems,

Table 1. Demographic characteristics of the study population

	Total (n = 700)	GA at scan <23 weeks (n = 84)	GA at scan 23.0–38.6 weeks (n = 511)	GA at scan ≥39 weeks (n = 105)
Maternal age, years	33.1±5.4	33.2±5.4	33.0±5.5	33.3±5.1
BMI	24.1±4.6	24.7±5.4	23.4±3.8	24.1±4.5
Caucasian	483 (69)	58 (69.1)	344 (67.3)	81 (77.1)
GA at scan, w.d.	31±6.4	21.3±0.9	30.6±4.7	40.4±0.8
Nulliparity	416 (59.4)	47 (56)	295 (57.7)	74 (70.5)
Previous SPTB	51 (7.3)	8 (9.5)	38 (7.4)	5 (4.8)
GA at delivery, weeks	39.6±1.3	39.4±1.2	39.0±2.1	40.6±0.7
Onset of labor				
Spontaneous	363 (51.8)	51 (60.7)	275 (53.8)	37 (35.2)
Induction	253 (36.1)	24 (28.6)	161 (31.5)	68 (64.7)
Elective CS	84 (12)	9 (10.7)	75 (14.7)	0 (0)
Mode of delivery				
Vaginal	489 (69.9)	62 (73.8)	359 (70.2)	67 (63.8)
Non-elective CS	128 (18.2)	13 (15.5)	77 (15.1)	38 (36.2)
Elective CS	83 (11.9)	9 (10.7)	75 (14.7)	0 (0)
Birth weight, g	3,228±575.2	3,324±396.8	3,155±615.7	3,464±410.7
Cervical length, mm	36±8.7	39.9±8.5	36.6±8.3	30.4±8.2

Data are given as the mean ± SD or n (%). GA = Gestational age; w.d. = week days; SPTB = spontaneous preterm birth; CS = Caesarean section.

Malvern, Pa., USA), Voluson 780 Pro, Voluson S6, Voluson E6, and Voluson E8 (GE Medical Systems, Milwaukee, Wis., USA) with a vaginal probe with a frequency between 2 and 10 MHz were used to acquire the images. Data were digitally collected in the original Digital Imaging and Communication in Medicine (DICOM) format and stored for off-line analysis in a custom-made program with a Graphic User Interface using MATLAB R2010b (version 7.11.0.584; MATLAB, The Mathworks Inc., Natick, Mass., USA). Images were acquired by experienced sonographers. The acquired images underwent a quality control process before delineation, according to the acquisition guide criteria. Cervical length was measured from the outer to the inner cervical os following the established guidelines [18]. The region of interest (ROI) was defined as the largest homogeneous region of the middle part of the anterior cervical lip. ROI delineation should avoid the cervical canal, the glandular area, and the internal and external cervical os (fig. 1b). Cervical length measurement and manual free hand delineation of the ROI were performed by two independent operators (N.B. and A.P.). Subsequently, the delineations were reviewed by a third operator (L.T.) in order to confirm that they met the delineation criteria.

Feature Extraction

Quantitative texture analysis was performed to extract features from the delineated ROI. Feature extraction was performed by means of a low binary pattern algorithm [19], concretely a multiresolution gray scale and rotation invariant approach mainly based on recognizing that local binary patterns are local image texture properties. A total of 18 cervical ultrasound features were obtained from each ultrasound image and ROI.

Statistical Analysis and Learning Procedure

Once features were extracted by quantitative texture analysis from cervical ultrasound images, a model of gestational age was developed following the next three steps: data splitting, feature transformation, and regression model computation. Regarding the statistical learning algorithm, the data were split into two bags. A cohort of women with gestational age at acquisition below 23 and above 39 weeks was included in bag 1a and bag 1b, respectively. The cohort of women between 23.0 and 38.6 weeks of gestational age was included in bag 2.

With respect to the feature transformation algorithm, feature selection and dimension reduction were performed from all bag 1 images in order to provide the most relevant features related to gestational age, since they represent both ends in the cervical remodelling process. Feature selection was performed by means of the ratio of the mean to standard deviation between extracted features. Once features were selected, the dimension reduction step was performed by means of principal component analysis.

Finally, a regression model was computed using bag 2 images to test the robustness and relevance of the transformed features extracted by the low binary pattern algorithm from bag 1 to quantify cervical texture changes. The random forest was the learning method used to train a regression model for estimating weeks of gestation. We ensured that the trained model was not over-fitted since the number of features used for training was less than one third of the sample size [20].

The model of gestational age based on features extracted by quantitative texture analysis was evaluated using regression fitting indicators such as the Pearson correlation (R^2) and root mean

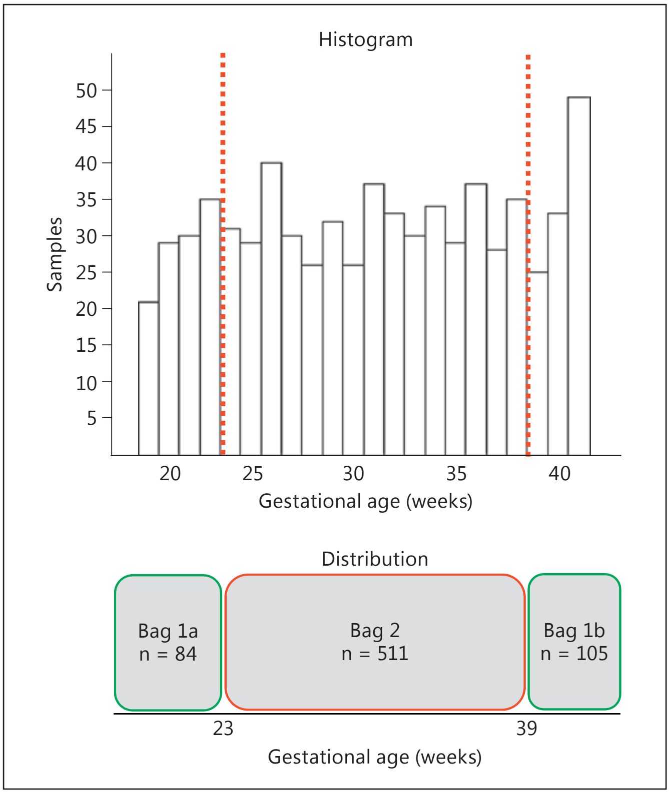

Fig. 2. Histogram and distribution of the final sample size.

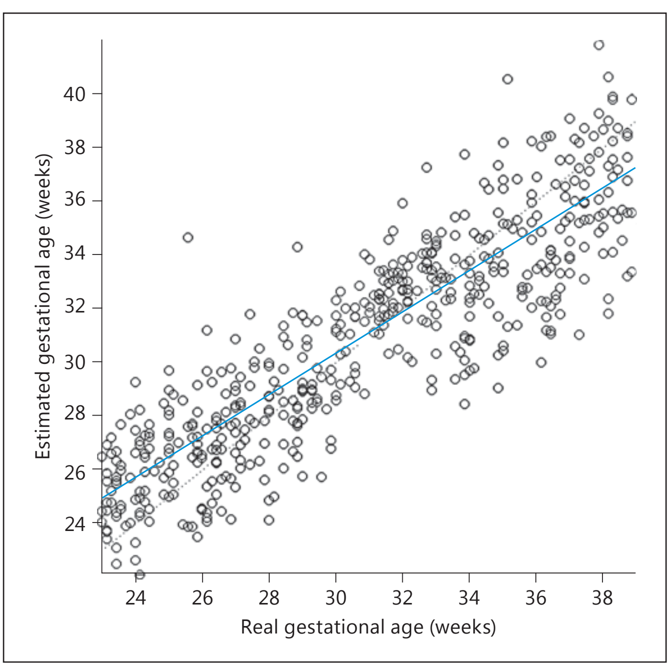

Fig. 3. Relationship between the estimated gestational age by quantitative analysis of cervical textures and the real gestational age. Pearson's correlation: R = 0.88.

square error. Lin's concordance correlation coefficient and the Bland-Altman plot were also used to test the agreement between the real and the estimated gestational age by texture analysis. Demographic characteristics were described as absolute and relative frequencies for qualitative variables and as the mean and standard deviation for quantitative variables. Additional clinical statistical analyses were computed with STATA/IC 13.0 (StataCorp 4905, College Station, Tex., USA). Statistical learning analyses were performed using MATLAB R2010b (version 7.11.0.584; MATLAB, The Mathworks Inc.).

Results

From March 2014 to January 2015, a total of 903 images from women with pregnancies between 20.0 and 41.6 weeks of gestation were acquired. After reviewing the perinatal outcomes, 49 women who delivered preterm were excluded, and 154 images were excluded after the image acquisition quality control. The main reason for exclusion was the presentation of a non-horizontal cervical canal. After ROI delineation, all images met the required criteria, and no re-delineations were necessary. Thus, 700 images with approximately 30 images per gestational week were finally included for analysis. The demographic characteristics and pregnancy outcomes of the study population are summarized in table 1.

The feature transformation algorithm obtained was first trained with the features from 189 images, 84 images below 23 weeks of gestation (bag 1a) and 105 images above 39 weeks of gestation (bag 1b). A regression model to correlate the features obtained with the gestational age was then evaluated in a large cohort of 511 images from between 23.0 and 38.6 weeks of gestational age. The sample distribution by weeks of gestation is shown in figure 2. There was a strong correlation between the real gestational age and the estimated gestational age by texture analysis (R = 0.88) as shown in figure 3. Lin's concordance correlation coefficient was 0.87, showing a high absolute agreement. The Bland-Altman interval of agreement was –0.13 (95% CI –4.52 to 4.26), with 3.52% of the cases over the limit, and 1.37% of the cases under the limit (fig. 4).

Cervical length was measured in the same cohort of images in which quantitative analysis of cervical ultrasound texture and regression model computation were performed (bag 2). The correlation between gestational age and cervical length measurements was R = –0.26 (fig. 5). Table 2 shows the correlation of the real gestational age with both the estimated gestational age by quantitative analysis of cervical texture and cervical length measurement.

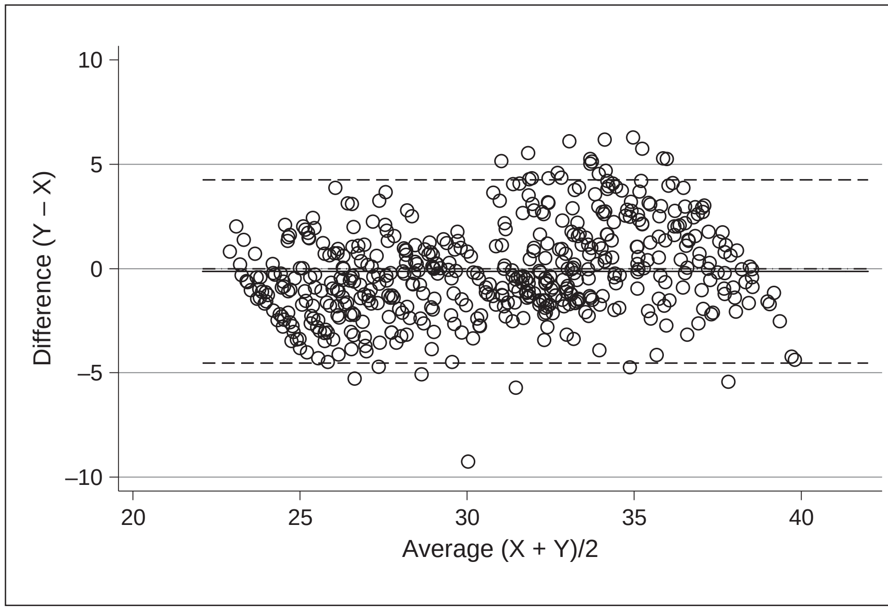

Fig. 4. Bland-Altman plot showing the agreement between the estimated gestational-age-by-texture analysis and the real gestational age.

Table 2. Correlation of the estimated gestational age by cervical texture and cervical length with the real gestational age in bag 2

	Pearson's correlation	R^2	RMSE
Cervical texture	0.88	0.77	2.24
Cervical length	–0.26	0.07	12.18

RMSE = Root mean square error.

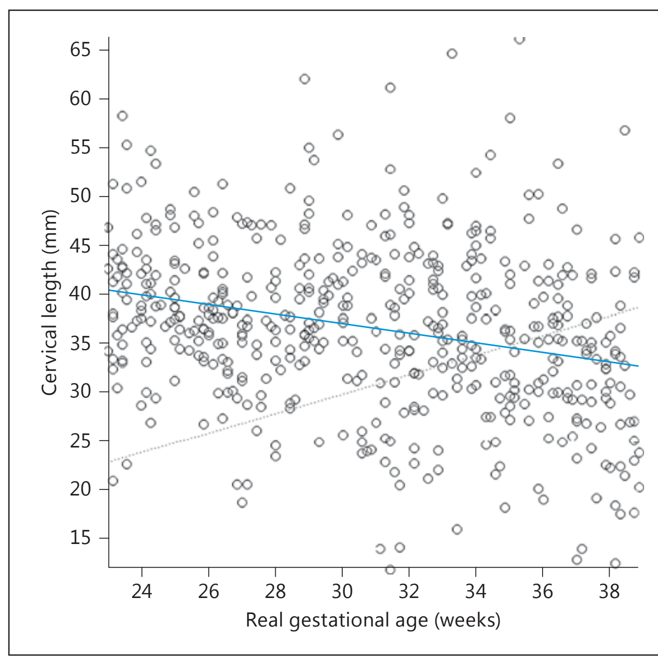

Fig. 5. Relationship between the cervical length and the real gestational age. Pearson's correlation: R = –0.26.

Discussion

This study provides evidence that quantitative analysis of cervical texture can feasibly extract features from cervical ultrasound images related to gestational age.

Pearson's correlation coefficient (0.88) and the Bland-Altman plot showed a good agreement between real gestational age and estimated gestational age by texture analysis. Considering that the cervical microstructure progressively changes throughout pregnancy until the time of delivery, gestational age could be assessed as a surrogate of these cervical changes. Assuming a certain degree of cervical structure variability within women of the same gestational age, the observed dispersion when comparing both approaches could be explained by this inherent biological variability. Therefore, the feasibility of quantifying cervical changes from 20.0 to 41.6 weeks of pregnancy represents a breakthrough in the detection of cervical remodelling by ultrasound.

The changes in quantitative analysis of cervical textures were also compared to the changes in cervical length throughout pregnancy in the same group of images. Cervical texture correlates much better with gestational age than cervical length (R cervical length = –0.26

vs. R cervical texture = 0.88). These results suggest that quantitative analysis of cervical texture is capable of detecting cervical changes during pregnancy, while cervical length is not, as it remains virtually stable. In line with our findings, several studies have reported few changes in cervical length throughout pregnancy, especially between 17 and 32 gestational weeks [21], with a high variability and dispersion between studies at the end of the pregnancy [22, 23]. Indeed, most of these studies showed a weak negative correlation between cervical length and gestational age [24, 25], which supports its limited usefulness in detecting early cervical remodelling.

The strength of the present study is the large number of images included, with a homogeneous distribution all throughout pregnancy. The demographic characteristics of all the patients as well as their perinatal outcomes were recorded in order to exclude patients who delivered preterm from the final sample. This guarantees that, from the clinical point of view, features were extracted from cervical images representing the expected cervical remodelling during a normal pregnancy.

This study presents some limitations. Firstly, the robustness in terms of using different scanner equipment and frequency probes was assumed. Although the robustness of these feature extractions and statistical learning procedures has already been proven in previous studies [16], further research with this specific setting is needed. Secondly, the ROI used in this study was selected because it is an easy delineation, as the anterior lip is always identifiable. Moreover, it avoids shadows and alterations produced by the cervical canal and mucus, since this region is the part of the cervix closest to the transducer. However, other ROI should be analyzed in order to evaluate the whole cervical structure with this same quantitative method and determine the most appropriate ROI.

In recent years, there has been a growing interest concerning the evaluation of uterine cervix properties in order to better understand its behaviour and its role throughout pregnancy. To date, elastography has been the method most studied, with several publications assessing its measurement standardization, reproducibility, and performance in the prediction of preterm birth risk and successful IOL. Elastography measures the percentage of tissue deformation occurring when oscillatory compression is applied, and this deformation can be expressed as *strain* [26, 27]. However, strain measurements and colour elastograms are related to the displacement of structures, which are directly related to the force exerted by the operator. Thus, a more objective method, independent of the pressure made by the operator, is necessary in order to obtain more reproducible results.

The cervical consistency index (CCI) assesses another biomechanical property of the uterine cervix, the maximum tissue deformability after manual compression of the cervix with the vaginal probe. Pressure is applied softly and progressively on the cervix until no further shortening of the anteroposterior diameter is observed. The CCI is a reproducible measurement, although the force applied to the tissue is also unknown [28]. The quantitative measure is calculated as the ratio between the anteroposterior diameter at maximum compression and the diameter at rest [29]. The CCI has shown a clear inverse linear relationship with gestational age. The CCI has also been found to be lower in women who delivered preterm and appeared to provide a better prediction of spontaneous preterm birth than cervical length [28]. Nonetheless, these findings need to be validated in a larger external cohort.

Other methods are able to assess cervical biomechanical characteristics such as distensibility and tissue stiffness [30–36], uterine cervix composition and optical characteristics [37–43]. Unfortunately, most of these methods are invasive and evaluate only a specific part of the cervix, which is an important limitation taking into account the heterogeneity of the uterine cervix structure.

The methods developed to date have demonstrated histological, biochemical, or biomechanical changes in the uterine cervix, but none have met the requirements to be implemented in clinical practice as predictive tools.

It is important to highlight that quantitative analysis of cervical texture by ultrasound overcomes most of these technical limitations, as it is an objective, non-invasive method, which does not require special equipment and training and could potentially evaluate the whole uterine cervix.

In conclusion, this study lays solid groundwork to explore quantitative analysis of cervical texture in clinical scenarios to evaluate cervical ripening and identify changes undetectable by cervical length or clinical examination. The feasibility of the quantitative analysis of cervical texture to detect changes throughout pregnancy facilitates its potential implementation to predict clinical outcomes, such as spontaneous preterm birth or failed IOL. Nonetheless, further research is needed to evaluate its ability as an image biomarker.

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Disclosure Statement

E.G. and M.P. have served as scientific advisors to Transmural Biotech S.L. All other authors declare no conflicts of interest.

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