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Inter- and Intraobserver Agreement in First Trimester Ultrasound Evaluation of Placental Biometry

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3D ultrasound · Perinatal outcome · Interobserver agreement · Frist trimester pregnancy · Placenta

Abstract
Objective: The aim of this study was to assess the clinical applicability of a new analytical software program by determining the inter- and intraobserver agreement for 2D placental biometry and three-dimensional (3D) placental volume (PV) in the first trimester. ***Methods:*** A prospective study of 25 singleton pregnancies between 11 and 14 weeks was conducted. 3D datasets were captured, and PV was estimated using the Phillips QLAB GI3DQ ultrasound quantification software. The basal plate (BP), chorionic plate (CP), placental thickness (PT), and the free uterine surface (FUS) area not occupied by placenta were considered for 2D biometry evaluation. Each variable was measured in 2 orthogonal planes with mean values used for the analysis. Intra- and interobserver agreement was evaluated. ***Results:*** Intraobserver agreement for both 2D and 3D measurements was high, particularly for the PV and PT (interclass correlation coefficient [ICC] 0.989 [95% confidence interval (CI) 0.97–0.99] and ICC 0.936 [95% CI 0.86–0.97], respectively). Interobserver agreement was good for the PV (ICC 0.963 [95% CI 0.91–0.98]), PT (ICC 0.822 [95% CI 0.63–0.91]), and CP (ICC 0.708 [95% CI 0.44–0.86]), but moderate for BP and FUS. ***Conclusions:*** PV, PT, and CP are reproducible measurements to evaluate first trimester placental biometry. Further research is needed to assess the clinical utility of these variables as predictors of poor obstetric outcomes.

Introduction

The placenta is an essential organ in pregnancy, playing a key role in fetus development and growth [1]. Impaired placental implantation and development have been consistently associated with adverse obstetric outcomes [2–5]. Despite the well-known relationship between a dysfunctional placenta and an increased risk of obstetric complications, specific placental evaluation has received substantially less attention than fetal examination.

Several different potential predictors of placental insufficiency have been described [6, 7]. First trimester placental volume (PV) has been correlated with birthweight [8,

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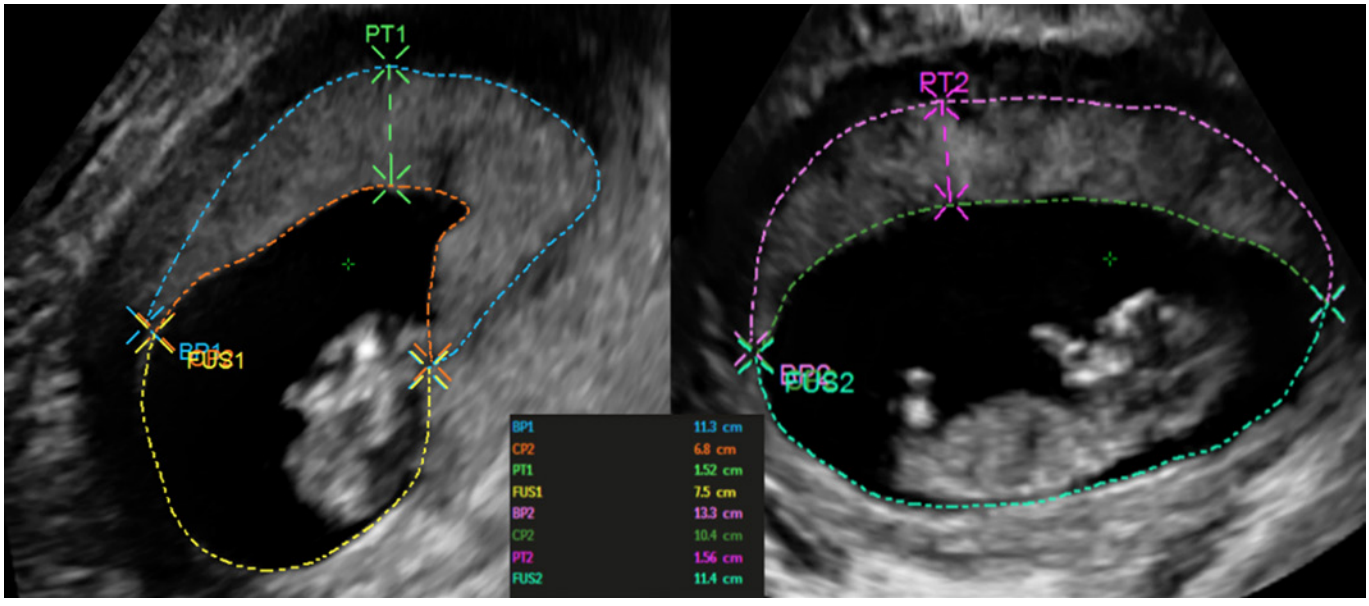

Fig. 1. Measurement of placental biometry with 2D ultrasound. All variables were measured at the largest view of the placenta in 2 orthogonal planes. BP, basal plate; CP, chorionic plate; PT, placental thickness; FUS, free uterine surface area not occupied by placenta.

9] and with second trimester uterine artery Doppler [10]. Rizzo et al. [11] also found that early-onset preeclampsia was associated with a significantly lower PV in the first trimester. Other studies have shown that the presence of a small PV at 11–14 weeks of gestation is associated with a higher risk of early-onset preeclampsia and impaired fetal growth [12]. Measurements obtained by two-dimensional (2D) placental sonography can also predict fetal growth. Schwartz et al. [13] demonstrated that patients with a thin placenta and a small chorionic plate (CP) in the second trimester had a higher risk of giving birth to a small-for-gestational-age infant. Another study found an association between first trimester basal plate (BP) surface area and fetal birthweight [14]. Although it has been suggested that algorithms evaluating the risk of placental insufficiency might benefit from the addition of 2D or three-dimensional (3D) measurements of the placenta [13], published data demonstrating the reproducibility of 2D placental biometry in the first trimester are scant. Moreover, to our knowledge, the internal and external validity of this approach has not been previously evaluated [15].

In the present study, we sought to evaluate the reliability of 2D and 3D placental biometry performed in the first trimester. We evaluated intra- and interobserver agreement of PV using a new quantification software (QLAB GI3DQ). We also assessed the intra- and interobserver reliability of 2D placental biometry.

Methods

This was a prospective study involving 25 singleton pregnancies presenting for first trimester ultrasound at 11–14 weeks of gestation at our institution (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain) between September and December 2016. Gestational age was determined according to the fetal crown-rump length. This was a planned analysis which was part of an ongoing research study to determine whether placental biometry combined with uterine artery Doppler and biochemical markers could predict preeclampsia and fetal growth restriction. This larger study was approved by the Ethics Committee of the Institutional Review Board at Hospital de la Santa Creu i Sant Pau and was registered with ClinicalTrials.gov, number NCT02879942. The first 25 patients included in this study were selected for this analysis.

Placental Sonography

One experienced obstetrician (C.T.) acquired all the datasets used for the analysis. To estimate the PV, 3D volume datasets of the placenta were acquired transabdominally using a commercially available ultrasound system (iU22 and Epiq7; Philips Healthcare). Each ultrasound system was equipped with an X6-1 PureWave xMatrix transducer with an extended operating frequency range (6–1 MHz) and a 90° × 90° volume field of view. For 3D captures, the 3D mode was activated and the region of interest was positioned over the uterus. The image was adjusted to aim the placenta perpendicularly. The sweep angle was set at 90°. For each patient, 2 or 3 3D volumes datasets were acquired. All volumes were scanned and saved. All images were then exported to an external hard drive for off-line analysis. For 2D evaluation of the placenta, the 3D datasets were used to scan the whole placenta in 2 orthogonal planes (the *X* plane and the *Y* plane), following the

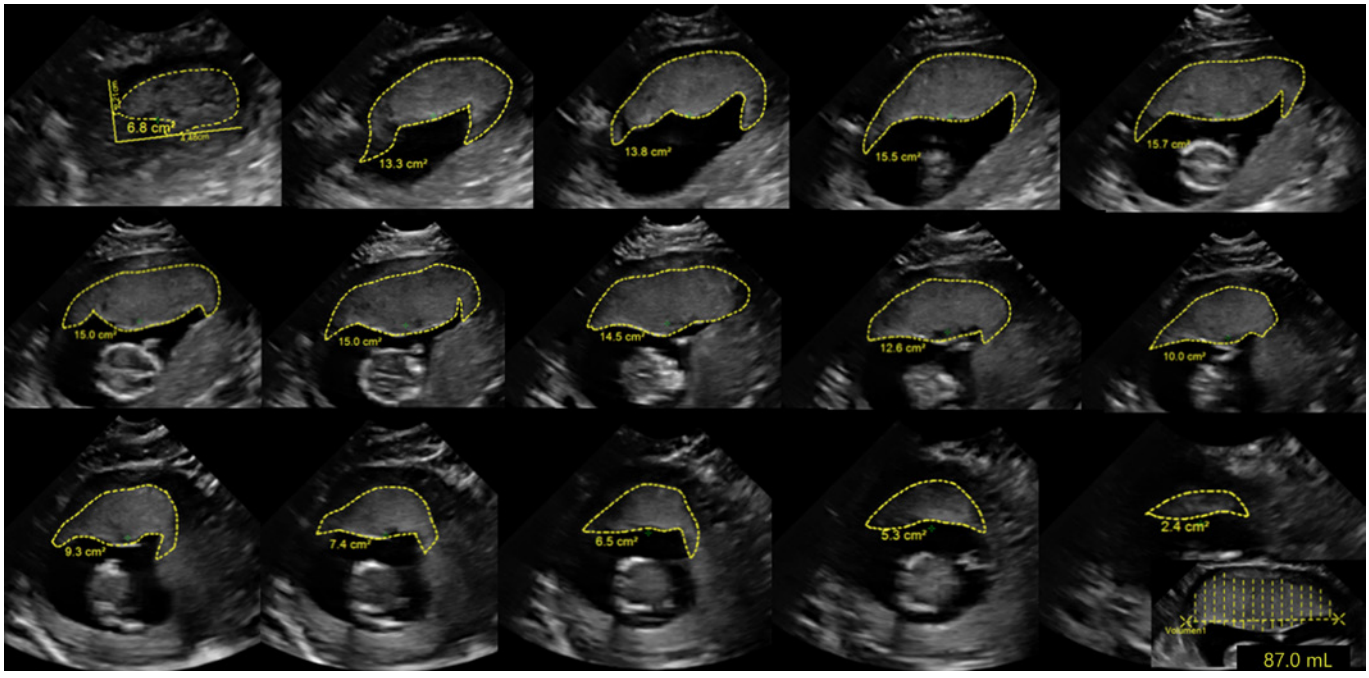

Fig. 2. Measurement of PV using 3D ultrasound: volume calculation using the QLAB GI3DQ software (15 slices). Each frame depicts the contoured area, manually traced, of the 15 slices of the placenta (the area of the selection is also indicated in each frame, in cm^2). PV, placental volume; 3D, three-dimensional.

methodology described by Schwartz et al. [13] First, the largest diameter in the *X* plane was identified, and this section was used to measure the 2D variables. Next, the *Y* plane was selected to scan again the placenta to determine the largest diameter for the 2D measurements. All measurements were performed by 2 experienced obstetricians (C.T. and M.C.M.), each with >5 years of experience in obstetric ultrasound and both certified by the Fetal Medicine Foundation to perform first trimester scans.

For the intraobserver analysis, all variables were calculated twice by observer 1 (C.T.). For the interobserver analysis, all variables were measured again by observer 1 and once by observer 2 (M.C.M.). Observer 1 performed the acquisition of all the datasets. The selection of the datasets used for the measurements and the selection of the 2D images was left to the clinical judgment of each observer. For the intraobserver analysis, a period of at least 1 week was respected between the 2 measurements. For the second measurements, the same procedure was followed: all 3D captures were evaluated to select the most suitable dataset, the 2D sections were selected after scanning the placenta in 2 orthogonal planes, and then, the 3D and 2D measurements were performed. Both observers were blinded to the results obtained in previous measurements.

2D Sonographic Variables

Four variables were considered in the 2D assessment of placental biometry, as follows: (1) the BP, the CP, placental thickness (PT), and the free uterine surface (FUS) – defined as the surface area of the uterus not occupied by the placenta-, all of which measured in 2 orthogonal planes as previously described (Fig. 1). The mean values of these measurements were used for the analysis. A curvilinear measurement was used to evaluate the BP, CP, and FUS; for the PT, a linear measurement was used. The BP was measured at the utero-placental interface, while the CP was measured along the fetal surface of the placenta. The PT was defined as the maximal thickness observed in the image, independently of the cord insertion site. Retroplacental veins were carefully excluded from the BP and PT measurements.

3D Placental Volume

The QLAB GI3DQ software (Philips Healthcare; Andover, MA, USA) was used to calculate the PV. This quantification software tool has both rendering and volume estimation capability. QLAB images are stored as DICOM sequences. The *X* plane was randomly selected as reference for the volume estimation. The 3D dataset was displayed on the *X* plane until the largest view of the placenta was visible. Then, the borders of the placenta were carefully traced and a linear axis was drawn, resulting in a diagram of 15 parallel sections perpendicular to the reference axis (Fig. 2). The outer contour of the placenta was manually traced in each slice, and all structures surrounding the placenta were carefully excluded. The manually traced contours automatically updated the intermediate frames, and the PV was automatically obtained when the last slice was traced.

Statistical Analysis

A dedicated database was created for the study. A spreadsheet format was used for the statistical analysis, which was performed with the IBM-SPSS software program, v.17.0 (IBM-SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess distribution normality for each variable. Interobserver and intraobserver reliability were assessed using two-way mixed interclass

Table 1. Maternal and pregnancy characteristics of the study cohort

	N = 25
Maternal characteristics	
Age (SD), years	33.1 (5.03)
Ethnicity, *n* (%)	
Caucasian	18 (72)
South American	5 (20)
Other	2 (8)
Mean BMI, kg/m^2 (SD)	25.72 (5.88)
Nulliparity, *n* (%)	17 (68)
Pregnancy characteristics	
Mean gestational age (SD), days	90 (3.9)
Placental location, *n* (%)	
Anterior	10 (40)
Posterior	9 (36)
Lateral	4 (16)
Fundal	2 (8)

SD, standard deviation.

correlation coefficients (ICCs) with 95% confidence intervals (CIs), paired Student's *t* test (P), and Bland-Altman plots. Agreement was categorized as moderate (ICC: 0.50–0.70), good (ICC > 0.70), or excellent (ICC > 0.9) [16]. Differences were considered statistically significant at $p < 0.05$.

Results

The mean gestational age at inclusion was 12 + 6 weeks, ranging from 11 + 6 weeks to 13 + 6 weeks. Visualization of the placenta was considered satisfactory in all cases for both the 2D and 3D measurements. The placenta was located anteriorly or posteriorly in 76% of cases; in the remaining cases, the placenta was located either laterally or fundally. Table 1 summarizes the maternal and pregnancy-specific characteristics of the patients included in the study. The mean time to calculate PV was 6 min and 59 s, and 2 min and 46 s were needed for the 2D measurements.

Intraobserver Reliability

The ICC was >0.70 for all study variables, indicating good to excellent agreement. The variables with the highest intraobserver reliability were the PV (ICC 0.989 [95% CI 0.97–0.99]) and the PT (ICC 0.936 [95% CI 0.86–0.97]). Table 2 summarizes the results of the intraobserver analysis. On the Bland Altman plots, no systematic bias between any paired measurements was detected. The differences between the 2 measurements of each variable did not increase with increasing placental size or volume (data not shown).

Interobserver Reliability

Table 3 summarizes the results for the interobserver reliability. The ICC was >0.7 for the PV and for 2 of the 2D variables (PT and CP). The highest interobserver reliability was obtained for the PV (ICC 0.963, 95% CI 0.91–0.98). Agreement for the remaining 2D variables was moderate (ICC: 0.50–0.70). On the Bland Altman plots, no systematic bias was observed between any paired measurements, and the degree of bias remained unaffected by PV or size (data not shown). Both observers considered that the datasets had a good quality for the measurements, and no particular difficulties were found.

Discussion

The results of the present study show that both intra- and interobserver agreement are excellent for first trimester measurements of 3D PV using the Philips QLAB GI3DQ software. Agreement (both intra- and interobserver) was also excellent for the 2D evaluation of the CP and PT.

Although intraobserver and interobserver reliability of PV in the first and second trimesters has been previously evaluated [17, 18], those studies used 2 different methodologies: the Virtual Organ Computer-aided AnaLysis technique (VOCAL) and the Multiplanar technique. VOCAL is a rotational technique based on predefined angles (12°, 18°, and 30°), while the Multiplanar technique (considered the gold standard [18]) uses parallel planes at fixed intervals (1 mm). By contrast, we used the QLAB GI3DQ quantification software (Philips Healthcare). This program is similar to the Multiplanar technique, except that a fixed number of slices are used. Previous reports have found that this software yields excellent reliability results in the determination of gastric volumes [19]. However, to our knowledge, our study is the first to use it to estimate PVs. Our findings show that the QLAB GI3DQ obtains agreement levels that are comparable to those reported with the VOCAL and Multiplanar approaches. These results may promote the greater use of placental biometry among clinicians, who could use whichever of these 3 programs is available in their clinical setting.

However, despite the good degree of agreement in the previously described methodologies, manual tracing of the placenta is still time-consuming. This is an important limitation for its widespread use. Recently, a new fully automated technique to estimate PV in the first trimester has been developed and validated [20, 21]. With this new technology, the authors have successfully overcome the problems of manual techniques, which remain both time-

Table 2. Intraobserver reliability for the sonographic measurements of BP, CP, PT, FUS, and PV

Variable[a]	Observation 1	Observation 2	Mean difference	SD	ICC	95% CI	*p* value
BP	13.63	13.73	−0.10	1.13	0.792	0.58–0.90	<0.001
CP	9.94	9.86	0.08	0.91	0.778	0.55–0.89	<0.001
PT	1.98	1.98	0	0.15	0.936	0.86–0.97	<0.001
FUS	9.45	9.52	−0.07	1.13	0.774	0.55–0.89	<0.001
PV	80.63	80.34	0.28	3.54	0.989	0.97–0.99	<0.001

BP, basal plate; CP, chorionic plate; PT, placental thickness; FUS, free uterine surface; PV, placental volume; ICC, intraclass correlation coefficient; SD, standard deviation; CI, confidence interval. [a] All measurements are given as mean values in centimeters, except for the PV (mL).

Table 3. Interobserver reliability for sonographic measurements of BP, CP, PT, FUS, and PV

Variable[a]	Observer 1	Observer 2	Mean difference	SD	ICC	95% CI	*p* value
BP	13.40	14.06	−0.66	1.64	0.682	0.39–0.84	<0.001
CP	9.62	10.15	−0.53	1.15	0.708	0.44–0.86	<0.001
PT	1.95	1.99	−0.04	0.28	0.822	0.63–0.91	<0.001
FUS	9.56	9.31	0.25	1.44	0.656	0.35–0.83	<0.001
PV	80.40	72.72	7.67	6.91	0.963	0.91–0.98	<0.001

BP, basal plate; CP, chorionic plate; PT, placental thickness; FUS, free uterine surface; PV, placental volume; ICC, intraclass correlation coefficient; SD, standard deviation; CI, confidence interval. [a] All measurements are given as mean values in centimeters, except for the PV (mL).

consuming and operator dependent. These technological advances have the potential to facilitate the incorporation of placental biometry in our clinical practice, as suggested in previous research [22].

Regarding the 2D variables, we also found good intra- and interobserver agreement for all the variables evaluated in the study. Agreement for the PT was excellent. In addition, interobserver agreement was good for CP evaluation. The strong intra- and interobserver reliability for the measurement of these 2 variables might have implications for their clinical applicability. In this regard, studies have shown that PT measurements obtained during gestation correlate with birthweight, but the interobserver and intraobserver reliability had not been evaluated, until now [23]. Our findings indicate that determination of both of these variables (CP and PT) is highly reproducible. However, further research is needed to confirm whether these values provide useful data to improve the prediction of adverse obstetric outcomes such as intrauterine growth restriction or preeclampsia.

In terms of interobserver agreement for BP and FUS, we found a trend toward good agreement, but the degree of agreement was only moderate when compared to the excellent levels of agreement obtained for the PT and CP. In contrast with our results, Suri et al. [14] found a high degree of interobserver agreement in the assessment of BP in the first trimester. In that study, BP correlated with birthweight at term; in addition, BP was significantly smaller in patients who developed preeclampsia. In our study, interobserver agreement for this variable was only moderate (ICC = 0.682), but very close to the cutoff to be considered "good." The difference between observers could be due to the difficulty of precisely identifying the edges of the placenta in the first trimester, although we believe that BP remains a promising variable for placental biometry assessment.

In our study, we defined a new variable (FUS) as a part of placental biometry evaluation. This measure is intended to be used as a ratio considering the placenta basal plate (BP/FUS). Following this rationale, we decided to measure FUS in the same plane where the largest placental diameter was visualized. We acknowledge that FUS could have been measured at its larger diameter, as described for the placental measurements. This would con-

stitute a different measurement that could be analyzed in further studies. The clinical usefulness of the ratio BP/FUS will be elucidated in the larger study.

For clinical purposes, we included 2D variables with a well-defined measurement methodology [13]. However, given the irregularities of the placental surface, we elected to use a curvilinear measurement rather than a linear or bilinear measurement. We also decided to evaluate placental biometry during the first trimester scan, as both aneuploidy and preeclampsia screening are conducted at this time and, thus, any variables with a high degree of reliability at this early stage of pregnancy are more likely to be addressed clinically.

The present study has several limitations. First, both observers were experienced obstetricians with specific training in the use of the QLAB GI3DQ software program. Although the skills needed to perform these measurements can be easily acquired, specific training is still necessary, and this could be an impediment for the immediate implementation of this method. Second, we did not compare our results to other methodologies commonly used to assess PV (VOCAL and Multiplanar) and, thus, cannot compare our findings to those widely used methods. However, this was not an aim of our study and, moreover, those software analyses are not available at our institution. Consequently, further research will be needed to compare the volume assessments obtained with the various methodologies. Third, mean BMI was 25.72 kg/m^2 and patients with a high BMI might have a poorer ultrasound imaging. However, the observers did not report any particular difficulties in the measurements, and it was the aim of this study to assess its reliability in usual clinical conditions. Finally, we did not record which dataset was used by the observers for the measurements. Although this information could be of interest, we believe it is unlikely that this factor may have affected our results.

Despite these limitations, our study has also several strengths. First, we believe that the use of a curvilinear measurement instead of a linear or bilinear measurement for 2D variables is an important strength. Given the placenta irregularities, a curvilinear measurement is more likely to yield an accurate result. Second, the selection of the 3D dataset and the selection of the 2D images were left to the clinical criteria of each observer, and thus, the results are more likely to be clinically reproducible. Even if all datasets were acquired by only 1 observer, the methodology to acquire the 3D dataset was very specific. Thus, very little variations should be observed between datasets, and it is unlikely that this factor may have overestimated the degree of agreement. Third, we included a new variable (FUS) as part of the placental biometry evaluation. Whether a larger or smaller uterine cavity relative to the placental size can affect placental growth or its development has not been previously investigated. However, the clinical relevance of this variable has yet to be determined.

Based on the findings presented here, we conclude that PV, PT, and the CP are all reliable and reproducible variables to evaluate placental biometry in the first trimester. However, more research is needed to determine the clinical value of these variables as potential predictors of adverse obstetric outcomes such as preeclampsia and fetal growth restriction.

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Statement of Ethics

This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Institutional Review Board at Hospital de la Santa Creu i Sant Pau and was registered with ClinicalTrials.gov, number NCT02879942. All the patients included in the study gave their written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contribution

Cristina Trilla was responsible for the inclusion of the patients. Both Cristina Trilla and Maria C. Medina performed the measurements that were analyzed in this study. Cristina Trilla wrote the submitted manuscript. Juan Parra supervised the compliance of the study protocol and participated in the training of the 2 investigators who performed the measurements. Elisa Llurba participated in the design of the study protocol, the statistical analysis, and in the redaction of the manuscript. Juan José Espinós participated in the design of the study protocol and supervised the redaction of the manuscript.

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