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ORIGINAL ARTICLE

Third trimester ultrasound soft-tissue measurements accurately predicts macrosomia

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Abstract

Objective: To evaluate the accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia.
Methods: Electronic databases were searched from their inception until September 2015 with no limit for language. We included only studies assessing the accuracy of sonographic measurements of fetal soft tissue in the abdomen or thigh in the prediction of macrosomia $\geq$34 weeks of gestation. The primary outcome was the accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia. We generated the forest plot for the pooled sensitivity and specificity with 95% confidence interval (CI). Additionally, summary receiver-operating characteristics (ROC) curves were plotted and the area under the curve (AUC) was also computed to evaluate the overall performance of the diagnostic test accuracy.
Results: Three studies, including 287 singleton gestations, were analyzed. The pooled sensitivity of sonographic measurements of abdominal or thigh fetal soft tissue in the prediction of macrosomia was 80% (95% CI: 66–89%) and the pooled specificity was 95% (95% CI: 91–97%). The AUC for diagnostic accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia was 0.92 and suggested high diagnostic accuracy.
Conclusions: Third-trimester sonographic measurements of fetal soft tissue after 34 weeks may help to detect macrosomia with a high degree of accuracy. The pooled detection rate was 80%. A standardization of measurements criteria, reproducibility, building reference charts of fetal subcutaneous tissue and large studies to assess the optimal cutoff of fetal adipose thickness are necessary before the introduction of fetal soft-tissue markers in the clinical practice.

Keywords

Diabetes, fetal weight, meta-analysis, review, ultrasound

History

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Introduction

Prenatal evaluation of the fetal weight is not always accurate, especially in fetuses with macrosomia. The term macrosomia is used to describe an overweight fetus or neonate. Even if there is no international consensus on the defection of macrosomia, the most common definition is birth weight $\geq$4000 g, which occurs in about 1–10% of all pregnancies [1]. A recent large high-quality population based cohort study from United States showed that a birth weight $\geq$4500 g in Whites or 4300 in Blacks and Hispanics is the optimal threshold to define macrosomia and that a birth weight $\geq$97th percentile, irrespective of race, is also reasonable to define macrosomia [2]. Fetal macrosomia is associated with an increased risk of perinatal morbidity and mortality. Large babies have an increased risk of intrapartum complications such as prolonged labor, shoulder dystocia with brachial palsy, asphyxia and facial nerve palsy [1]. Women with diabetes or gestational diabetes mellitus (GDM) are at increased risk of fetal macrosomia [1,2].

A recent meta-analysis has shown that two-dimensional (2D) ultrasound estimated fetal weight (EFW), based on a combination of sonographic fetal measurements, was an overall poor predictor of fetal macrosomia and that magnetic resonance imaging (MRI) volumetry to estimate fetal weight appeared to be much more sensitive than 2D ultrasound EFW for predicting fetal macrosomia [3]. Evaluation of fetal soft tissue has been recently proposed to improve birth weight prediction by ultrasound and it has been shown that the precision of EFW may be improved by adding fractional limb volume measurements to conventional 2D ultrasound biometry.

The aim of this systematic review and meta-analysis was to evaluate the accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia.

Methods

This review was performed according to a protocol designed *a priori* and recommended for systematic review [4]. Electronic databases (MEDLINE, PROSPERO, Scopus, ClinicalTrials.gov,

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EMBASE, Sciencedirect, the Cochrane Library; Scielo) were searched from their inception until September 2015 with no limit for language. Search terms used were the following text words: ''macrosomia,'' ''ultrasound,'' ''fetal weight,'' ''EFW,'' ''diabetes,'' ''large for gestational age,'' ''shoulder dystocia;'' ''pregnancy;'' ''MRI;'' ''2D;'' ''3D;'' ''accuracy;'' ''systematic review; ''meta-analysis,'' ''metaanalysis,'' ''prediction,'' ''birthweight,'' ''biometry,'' ''limb,'' ''obstetric,'' ''volume'' and ''soft tissue.'' No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (GMM, GS). Differences were discussed and consensus reached.

We considered randomized controlled trials, case–control and cohort studies. Studies were included if they reported data allowing construction of a 2×2 table. We included only studies assessing the accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia at $\geq$34 weeks of gestation. Only studies that measured fetal soft tissue in the abdomen or thigh were included. The primary outcome was the accuracy of sonographic measurements of fetal soft tissue in prediction of macrosomia, as defined in the original studies.

Data abstraction and methodological quality of the included studies were completed by two independent investigators (GMM, GS). Each investigator independently abstracted data from each study separately. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Disagreements were resolved by consensus with a third reviewer (PM). All authors of the original studies were contacted for missing data if possible.

The quality assessment of each included study was assessed by using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria [5]. The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyzes (PRISMA) statement [6]. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42015026372) following the PRIMA guidelines for protocols (PRIMSA-P) [7].

For all the included studies, we constructed a 2×2 table cross-classifying ultrasound measurement of fetal soft tissue and the prediction of macrosomia. We generated the forest plot for the pooled sensitivity (i.e. detection rate) and specificity with 95% confidence interval (CI). The forest plot, also known as a bloobbogram, is a graphical display of estimated results and pooled data from the studies included in the meta-analysis [4].

Additionally, symmetric summary receiver-operating characteristics (sROC) curves were plotted. sROC analysis is a recently developed statistical technique that can be applied to meta-analysis of diagnostic tests [8]. The area under the curve (AUC) and the Q^* index were also computed to evaluate the overall performance of the diagnostic test accuracy. The AUC of an sROC curve is a measure of the overall performance of a diagnostic test in accurately differentiating those cases with and those without the condition of interest. The Q^* index is defined by the point at which sensitivity and specificity are equal, which is closest to the ideal top-left corner of the sROC space. Both values range between 0 and 1, with higher values indicating better test performance [8]. The following guidelines have been suggested for the interpretation of AUC values: low ($0.5 \geq$ AUC <0.7), moderate ($0.7 \geq$ AUC <0.9) or high ($0.9 \geq$ AUC ≤ 1) accuracy [8]. We planned to assess the AUC in subgroup analysis according to the fetal soft tissue used. We also planned to assess an indirect meta-analysis to compared to AUC between the different fetal soft tissue used by the original studies.

Given that the individual estimates of treatment effect would vary by chance and some variation is expected; the degrees of between-study heterogeneity were evaluated by using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of $\geq$30% indicate a substantial level of heterogeneity [4,9].

Potential publication biases were assessed statistically by using Begg's and Egger's tests and by using the Deeks' asymmetry test for publication bias [4,9].

The data analysis was completed independently by authors (GMM, GS) using Meta-DiSc 1.4 (Zamora). The completed analyses were then compared, and any difference was resolved with review of the entire data.

Results

The flow of study identification is shown in Figure 1. Three prospective cohort studies, including 287 women, were

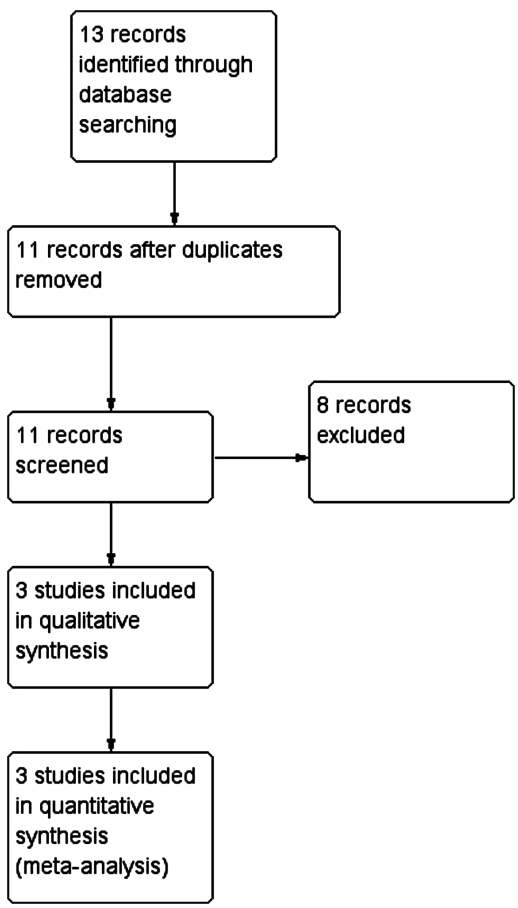

Figure 1. Flow diagram of studies identified in the systematic review.

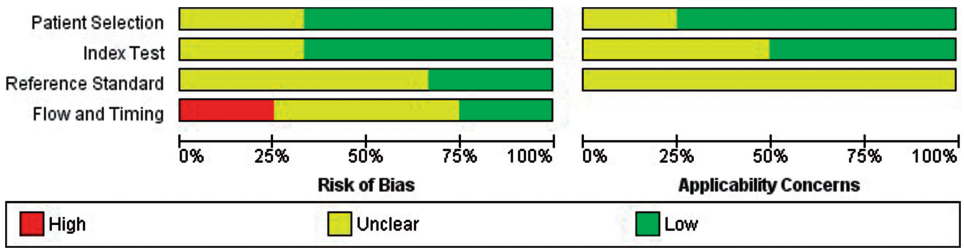

Figure 2. Review authors' judgment of risk of bias and applicability concerns based on Quality Assessment of Diagnostic Accuracy Studies tool presented as percentages across included studies.

Table 1. Characteristics of the included studies.

	Petrikovsky 1997[12]	Grabedian 2013[10]	Pagani 2014[11]
Location	USA	France	Italy
Study Design	Prospective cohort	Prospective cohort	Prospective cohort
Inclusion criteria	Singletons	Singletons with diabetes mellitus	Singletons with GDM
Sample size	133	29	125
Soft-tissue thickness	Abdominal subcutaneous tissue thickness ≥11 mm	Abdominal subcutaneous tissue thickness ≥11 mm	TVol
GA at measurements (weeks)	37–42	34	34–36
Other sonographic measurements	Not reported	Fetal biometry, liver size, STT, STA, STS	Fetal biometry
Primary outcome	Prediction of macrosomia	Prediction of macrosomia	Prediction of macrosomia
Definition of macrosomia	Birthweight >4000 g	Birth weight >90th percentile	Birthweight >4000 g

GA, gestational age; GDM, gestational diabetes mellitus; TVol, fractional thigh volume.

analyzed [10–12]. Publication bias, assessed using Begg's and Egger's tests, showed no significant bias ($p = 0.62$ and $p = 0.71$, respectively). Deeks' test showed no significant asymmetry ($p = 0.88$). The statistical heterogeneity between the included studies was low ($I^2 = 0\%$). Figure 2 shows the results of the quality assessment presented as percentages across the studies. None of them had high risk of bias in patient selection and index test. Table 1 shows the characteristics of the included studies. All of them were prospective cohort studies, included only singleton gestations, and excluded multiple pregnancies. Two studies came from Europe [10,11], and one from United States [12]. While Petrikovsky et al. included all women with singleton gestations [12]; the other two studies included only singletons with an increased risk of macrosomia [10,11]: Pagani et al included only women with GDM [11], and Grabedian et al. included only women with pregestational diabetes [10]. The method of ultrasound ascertainment was clearly described in all the individual studies. In one study, all examinations were performed with an Acuson XP128/10 using a 3.5 MHz and 5 MHz curvilinear probe, the fetal abdominal subcutaneous tissue thickness was measured in the anterior third of the abdominal circumference by placing the cursor at the outer and inner edges of the echogenic subcutaneous fat line [12]. Grabedian et al used a 5 MHz curvilinear probe to measure the abdominal subcutaneous tissue thickness [10]. In the Italian study, all ultrasound examinations were performed by using a conventional transabdominal two-dimensional (2D) scan in order to obtain the EFW, while 3D volumes were acquired from the thigh to obtain fractional thigh volume (TVol) [11].

From all the included studies, we were able to construct a 2×2 table for the prediction of macrosomia by using sonographic measurements of fetal soft tissue. Pooled results from the meta-analysis showed that sensitivity of sonographic measurements of fetal soft tissue in the prediction of macrosomia ranged from 70% to 87% and specificity from 79% to 96%. The pooled sensitivity (i.e. detection rate) was 80% (95% CI: 66–89%) and the pooled specificity was 95% (95% CI: 91–97%). The pooled positive predictive value and the pooled negative predictive value were 78% (95% CI: 67–85%) and 95% (95% CI: 89–92%), respectively. The AUC for diagnostic accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia was 0.92 and suggested high diagnostic accuracy (Figure 3). The AUC was high in both subgroup analysis of only studies on abdominal fetal soft tissue (AUC = 0.90) and of only studies on thigh fetal soft tissue (AUC = 0.93). The indirect meta-analysis showed that the TVol had a significantly higher detection rate compared to abdominal fetal soft tissue ($p < 0.0001$).

Discussion

This systematic review and meta-analysis, assessing the accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia, showed that third-trimester sonographic measurements of fetal soft tissue may help to detect macrosomia. Particularly, our findings showed that fetal soft tissue has high diagnostic accuracy in the prediction of macrosomia. The pooled detection rate was 80%.

Our study has several strengths. This may be the first meta-analysis evaluating the accuracy of sonographic measurements of fetal soft tissue in the prediction of macrosomia. No similar meta-analyses were found during the systematic review. The overall risk of bias of the included studies was low. All the included studies had the same primary outcome, that is, the prediction of macrosomia. The protocol of this review was *a priori* registered on PROSPERO.

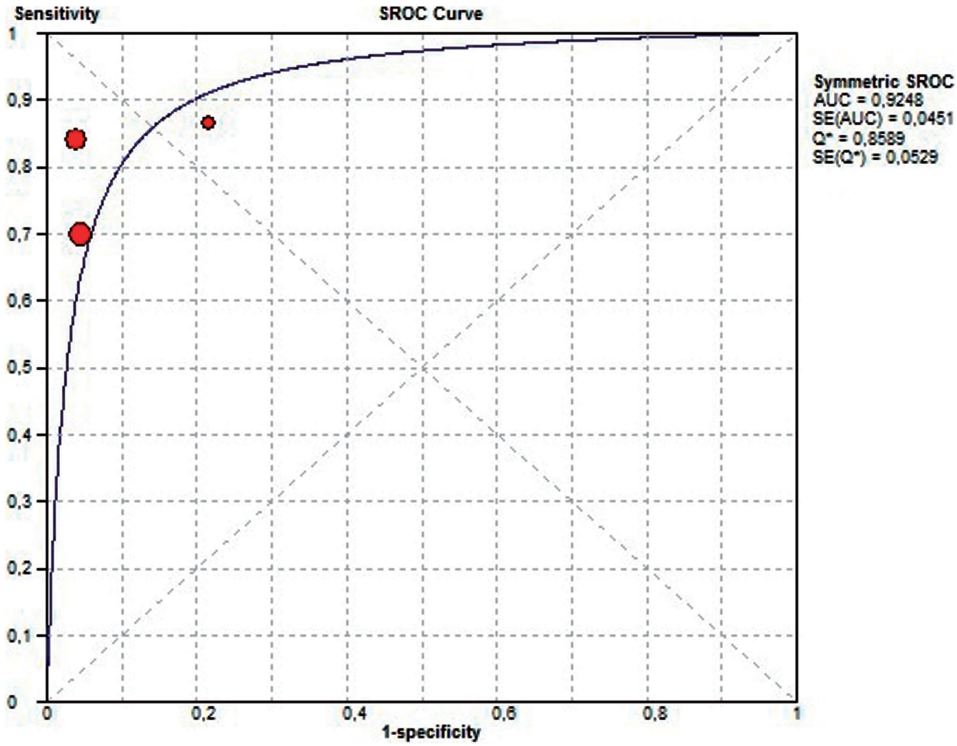

Figure 3. Symmetric summary receiver operating characteristics curve with 95% confidence interval for the accuracy of sonographic measurements of fetal soft tissue in prediction of macrosomia. Area under the curve (AUC) ± standard error (SE) = 0.925 ± 0.05; Q^* ± SE = 0.859 ± 0.05.

Statistical tests showed no significant potential publication biases. The statistical heterogeneity between the included studies was low with no inconsistency in the pooled results ($I^2 = 0\%$).

Limitations of our study are mostly inherent to the limitations of the included studies. All the included studies were cohort studies and had different inclusion criteria. The soft-tissue markers used were different: Pagani et al. reported the accuracy of TVol-based methods for the prediction of macrosomia in gestational diabetic pregnancies, while the other two studies used abdominal subcutaneous tissue thickness (Table 1). The number of the included women and the number of the included studies were limited and for this reason assessing subgroup and sensitivity analysis according to inclusion criteria and according to the soft tissue used were not feasible. The predictive values of a given markers may significantly vary across the gestational age range from 34 to 42 weeks. Unfortunately, since none of the included studies stratified for and reported data by gestational age, a subgroup analysis according to gestational age was not feasible. The predictive values are dependent on the prior probability of an event happening, and therefore, they cannot be generalized for the whole pregnancy interval covered by this meta-analysis. The generalizability and the external validity of these findings may be limited due to the quality of ultrasound employed at these institutions and the patient population evaluated. No adjustment for potential confounders were made by the original studies. The sample size was small and this is a major shortcoming of the meta-analysis. The three selected studies have in common that they analyzed fetal soft tissue in the prediction of macrosomia in singleton pregnancies, but they are not comparable in other terms, such as geographical areas with significant nutritional and anthropometric differences, inclusion or exclusion of diabetes and different fetal soft tissues under study.

Management of macrosomia provides a challenge in modern obstetrics. Studies about macrosomia are limited by their retrospective design, by the nonuniform definition of macrosomia, and because they are not randomized. So far, the role of the ultrasound in the definition, diagnosis and management of macrosomia is debate. Various methods based on regression analysis, decision trees and clinical risk score have been proposed [13–15]. The current tools available to predict fetal macrosomia perform poorly [3]. Ultrasonography examinations are commonly used to estimate fetal weight and to predict macrosomia. A recent meta-analysis has shown that 2D ultrasound fetal biometry was an overall poor predictor of fetal macrosomia [3]. Complementary methods for the prenatal assessment of generalized nutritional status may also be possible beyond the use of EFW as well. In 2009, Lee et al. provided normal reference ranges for fetal soft tissue as a new index of generalized fetal nutritional status and reported technical considerations for this technique [16]. They showed that fetal soft tissue, such as fractional limb volume assessment, may improve the detection and monitoring of malnourished fetuses [16]; and so sonographic measurements of fetal soft tissue has been recently proposed in the prediction of macrosomia [10–12,16]. Being able to predict macrosomia has several potential benefits because failure to detect it may be associated with higher rates of neonatal morbidity and mortality [1,2,17]. Providers and birth locals may be able to better plan staff and coverage [17].

In summary, third-trimester sonographic measurements of fetal soft tissue after 34 weeks may help to detect macrosomia with a high degree of accuracy and an 80% of detection rate.

Fetal soft tissue as a screening test for the prediction of macrosomia may be best considered in women who might most benefit from this test. A standardization of measurements criteria, reproducibility, building reference charts of fetal subcutaneous tissue and large studies to assess the optimal cutoff of fetal adipose thickness are necessary before the introduction of fetal soft-tissue markers in the clinical practice.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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