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Ultrasound prediction of spontaneous abortions in live embryos in the first trimester

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ABSTRACT

Objective: To generate a prediction model for miscarriage in women with a viable single pregnancy from first-trimester ultrasound findings and maternal characteristics.
Methods: A prospective, cross-sectional study of 415 singleton pregnancies was performed. The initial ultrasound parameters were crown-rump length (CRL), mean gestational sac diameter (MGSD), yolk sac diameter (YSD), and the sum of the differences between gestational ages and embryonic heart rate (EHR). Potential predictors for spontaneous miscarriage occurring prior to 20 weeks were evaluated.
Results: Fifty-three (12.8%) patients had miscarriages and 362 (87.2%) had normal outcomes. Forty-three (81.2%) miscarriages occurred in the first trimester, 5 (9.4%) in the second trimester, and 5 (9.4%) represented fetal anomalies. EHR, CRL, and MGSD were decreased in the miscarriage group (p<0.001); YSD showed no difference (p=0.21). Gestational age by CRL and by MGSD were different between the groups (p<0.001). The proposed sum of differences was higher in the miscarriage group (p<0.001). Maternal age, indication for scan, gestational age by MGSD and CRL, heart rate, and proposed sum of differences were found to be potential predictors. Predictive ability of our proposed model was calculated sensitivity as 0.509, and specificity as 0.975 with a cut-off=0.5. The prediction model's false positive rate is 0.025, and its false negative rate is 0.491.
Conclusions: Miscarriage can be predicted via maternal characteristics and ultrasound findings. Advancing maternal age, low EHR, and high proposed sum of differences increase the probability of miscarriage.

Keywords: ultrasound, prediction, abortion, first trimester, pregnancy

INTRODUCTION

Localization and viability of pregnancy, as well as multiple pregnancies, can be identified through detailed sonographic evaluation of the choriodecidua and embryo in the first trimester. In addition, complications of early pregnancy, including reabsorbed early pregnancy, retrochorionic hemorrhage, incomplete abortion, and complete abortion can be assessed through such evaluation. The position of the gestational sac and regularity of the choriodecidua, yolk sac, embryo, adnexa, and cul-de-sac should be assessed during this examination. Furthermore, data related to the prognosis of pregnancy can also be obtained as a result of this evaluation.

Detection of fetal heartbeat in the first evaluation does not assure a healthy prognosis of pregnancy, even in patients without any complaints. The incidence of spontaneous abortion following sonographic detection of embryonic heart motion is high, ranging from 5 to 20% (1, 2).

The double sac of gestation formed by the developing primary yolk sac and extraembryonic coelom, surrounded by echogenic choriodecidua, can be seen in the fifth gestational week (3). In general, the yolk sac can be visualized when the gestational sac reaches 1 cm, while the embryo localized in proximity to the secondary yolk sac can be seen when the sac reaches to a size of 1.5 cm.

A yolk sac that has grown above ≥5 mm visualized before the 7th week of gestation is associated with embryonic death as in the impaired and small ones (4, 5). Several parameters, such as the heart rate and the ratio of crown-rump length (CRL) to the gestational sac (GS), may provide data about the prognosis of pregnancy (6). The heart rate progressively increases to 110 from 175 beats per minute after gestational weeks 5 and 9 (7). Heart rates under 85 beats per minute are associated with disruption of pregnancy and require follow-up sonograms (8). Another parameter that is considered to have a prognostic value is discordance between the CRL and the gestational sac. Overgrown (9) or smaller than gestational week sacs (10) may be related to abortion.

Sonographic criteria to distinguish abnormal pregnancies that will result in abortion from normal pregnancies in the case of early live pregnancy are yet to be established. The objective of this prospective study was to compare ultrasonographic (USG) findings including mean gestational sac diameter (MGSD), embryonic heart rate (EHR), and yolk sac diameter (YSD) corrected for CRL at 6–10 gestational weeks in singleton pregnancies that resulted in abortion and those continued until term with normal live births, to identify a model for predicting subsequent abortion with the best diagnostic accuracy and to determine sonographic criteria that will distinguish abnormal pregnancies that will result in abortion from normal pregnancies in the case of early live pregnancy.

PATIENTS AND METHODS

This prospective cross-sectional study was conducted between January 2014 and June 2015 with spontaneously conceived live singleton pregnancies at 6–10 gestational weeks. The following characteristics were recorded for each pregnant woman: age; obstetric history (parity, prior history of abortion); systemic disease; smoking status; characteristics of the menstrual cycle in the last 3 months before the conception; and symptoms of the current pregnancy indicating threatened miscarriage, such as lower abdominal pain, vaginal bleeding and subchorionic hematoma on USG, and hospitalization due to threat of abortion.

Expected gestational age (EGA) was determined by last menstrual period (LMP). Observed gestational age (OGA) was determined by CRL. Concordance between USG and gestational

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Table 1: *Demographic characteristics and other indications for the normal outcome and miscarriage groups*

	Normal Outcome (n=362)	Miscarriage (n=53)	*p*
Maternal age in years, mean±SD	27.19 ± 5.32	29.21 ± 6.56	**0.01**
Gestational age weeks, mean±SD	54.81 ± 8.32	55.89 ± 7.62	0.38
Smoker, n (%)	17 (4.7)	3 (5.7)	0.76
Parity, n (%)			0.12
Nulliparous	124 (34.4)	24 (45.3)	
Parous	238 (65.7)	29 (54.7)	
Indication for scan, n (%)			**<0.001**
None	253 (69.9)	22 (41.5)	
Spotting bleeding	51 (14.1)	9 (17.0)	
Heavy bleeding	2 (0.6)	11 (20.8)	
Subchorionic hematoma	6 (1.7)	0 (0)	
Pelvic pain only	39 (10.8)	8 (15.1)	
Double vaginal bleeding and subchorionic hematoma	11 (3)	3 (5.7)	
Hospitalization, n (%)	46 (12.7)	16 (30.2)	**0.001**
Past history of spontaneous miscarriage, n (%)	131 (36.2)	22 (41.5)	0.453
Dating, n (%)	63 (17.4)	20 (37.7)	**0.001**

week (EGA and OGA) was checked in patients with regular menstrual cycles before pregnancy and knew the date of their last menstruation. Differences in days between the estimated and observed gestational ages were determined for each patient. Patients who had multiple pregnancy, conceived using assisted reproductive technology (ART), dead embryo, ectopic pregnancy, anembryonic pregnancy, and complete or incomplete abortion at the first presentation were excluded from the study.

The first scans were performed transabdominally to identify embryonic life at various gestational ages from as early as 42 days onwards, as directed by a specialist. Embryonic life, number of pregnancies, and pregnancy location, as well as CRL, MGSD, YSD, and her, were obtained from the ultrasound findings recorded at the first scan. The MGSD was calculated in millimeters as the average of three orthogonal planes measured from the inner sac wall/chorionic fluid interface. The CRL was measured to the nearest millimeter from the outer ends of the embryo (greatest length). Besides gestational age based on LMP (menstrual age, MA) and corresponding gestational age with nomogram through CRL and MGSD measured in millimeters was determined for each pregnant woman. As a result, three separate gestational ages were obtained in days based on MA, CRL, and MGSD. MA was equalized to the gestational age by CRL in patients who had irregular menstrual cycles or did not remember their LMP. Then, the sum of the differences among these three separate gestational ages was calculated using the following formula:

Proposed sum of the differences between gestational ages = [MA – CRL age difference (real value)] + [MA – MGSD age difference (real value)] + [MGSD age – CRL age (absolute value)]

The EHR was calculated as beats per minute using the ultrasound machine's software after measurement of the distance between two heart waves on a frozen M-mode image with electronic calipers. The YSD was calculated using calipers placed at the center of the yolk sac wall. All sonographic scans were carried out by appropriately trained doctors with a Voluson P8 (GE Ultrasound, Korea) using 3.5 MHz transabdominal transducers for B-mode imaging.

Ultrasonographic images of the first scan were archived in all patients, who were then followed-up until birth. The pregnant women were divided into two groups as the patients who experienced spontaneous abortion (miscarriage group) and those who had a live birth (normal outcome group). USG findings were compared between these two groups. The study protocol was approved by the Clinical Research Ethics Committee (Ref. No. 26857650/105), and written informed consent was obtained from all the participants prior to enrolling to the study.

Statistical Analysis

Comparisons of patient characteristics in the normal outcome and miscarriage groups were performed using the t test when the data were unimodal, the Mann–Whitney U test when the data deviated greatly from normality [those data are displayed as median (1st quartile(Q1)–3rd quartile (Q3))], or the Chi-square test for categorical data. Simple and multiple logistic regression models were used to evaluate the predictive abilities of potential predictors (maternal age, parity, indication for scan, gestational age by last menstruation date, gestational age by CRL, gestational age by MGSD, YSD, EHR, proposed sum of differences between gestational ages). Predictive abilities were evaluated using receiver operating characteristic (ROC) curves that were drawn for EHR, proposed sum of differences, and proposed final model. Sensitivity, specificity, area under the ROC curve (AUC), and cut-off values were given. A classification tree was developed using the QUEST algorithm and 10-fold cross-validation. The Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses. *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 415 live single pregnant women who underwent a first-trimester transabdominal ultrasound scan were included over the study period. The data search identified 53 (12.8%) patients fulfilling the entry criteria for the miscarriage group and 362 (87.2%) for the normal outcome group of these pregnancies, which formed the basis of our analyses. Forty-three of 53 miscarriages (81.2%) occurred in the first trimester of pregnancy, 5 (9.4%) occurred in the second trimester, and 5 (9.4%) represented fetal anomalies. Mean maternal age of all the patients included was found to be 27.45±5.53 years, while mean gestational age corrected by LMP or CRL at the first scan was found to be 54.95±8.23 days. Sixty-two (14.9%) patients were hospitalized due to signs and symptoms of the threat of miscarriage. Of all pregnant women, 332 (80%) had regular menstrual cycles, remembered their LMP, and had a gestational age concordant with CRL; meanwhile, 83 (20%) patients exhibited a gestational age discordant with CRL or did not know their LMP. Gestational age was determined by CRL in the latter patients.

Table 1 displays a comparison of patient characteristics between the normal outcome and miscarriage groups. Mean maternal age was higher in the miscarriage group (p=0.01). Gestational age, smoking status, and parity were not different between the two groups (p=0.38, p=0.76, and p=0.12, respectively). Distributions of the indication for scan were different between two groups (p<0.001), and heavy bleeding was observed in 20% of patients in the miscarriage group compared to 0.6% of patients in the normal outcome group. Percentages of hospitalization and dating were higher in patients in the miscarriage group than those in normal outcome group (p=0.001, each).

Table 2 represents the measures related to USG findings of the two groups. EHR, CRL, and MGSD were decreased in the miscarriage group compared to normal outcomes (p<0.001, each). YSD was not different between the two groups (p=0.21). Gestational age by CRL and gestational age by MGSD were different between the two groups (p<0.001, each). The proposed sum of differences was higher in the miscarriage group (p<0.001).

To evaluate predictive abilities of potential predictors, we created simple logistic regression models (Table 3). Maternal age, indication for scan, gestational age by MGSD, gestational age by CRL, heart rate, and proposed sum of differences were found to be potential predictors (significant *p*-values), whereas

Table 2: *EHR, CRL, MGSD, YSD, and gestational ages by CRL and MGSD in the normal outcome and miscarriage groups*

	Normal Outcome (n=362)	Miscarriage (n=53)	*p*
EHR bpm	156 (145–172)	122 (84.5–145)	**<0.001**
CRL mm	10 (6.16–17.31)	5.68 (3.92–10.69)	**<0.001**
MGSD mm	33.05±10.71	24.23±8.87	**<0.001**
YSD mm	4.25±0.75	4.49±1.40	0.213
GA by CRL day	50 (45–57)	44 (43–50)	**<0.001**
GA by GSD day	57.73±10.24	49.32±8.97	**<0.001**
Proposed sum of differences	6 (0–14)	22 (10–32)	**<0.001**

Unimodal data is given as mean±SD and non-normal data as median (Q1–Q3). GA: Gestational age

Table 3. *Simple and multiple logistic regression results for potentially important variables to predict miscarriage*

	Simple		Multiple	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Maternal age (years)	1.07 (1.01–1.12)	**0.01**	1.09 (1.01–1.17)	**0.034**
Parity*	1.58 (0.88–2.84)	0.12		
Indication for scan*		**<0.001**		0.054
Spotting bleeding	2.03 (0.88–4.66)	0.095	1.82 (0.62–5.31)	0.26
Heavy bleeding	63.25 (13.18–303.52)	**<0.001**	30.40 (3.68–251.25)	**0.002**
Subchorionic hematoma	0 (0)	0.99	0 (0)	0.99
Pelvic pain only	2.36 (0.98–5.67)	0.055	1.57 (0.48–5.17)	0.46
Double vaginal bleeding and subchorionic hematoma	3.14 (0.81–12.08)	0.09	2.93 (0.50–17.01)	0.23
Gestational age by LMP (days)	1.01 (0.98–1.05)	0.37		
Gestational age by GSD (days)	0.91 (0.89–0.95)	**<0.001**	0.99 (0.95–1.05)	0.96
Gestational age by CRL (days)	0.89 (0.84–0.94)	**<0.001**	0.92 (0.84–1.01)	0.084
Yolk sac (mm)	1.36 (1–1.85)	0.053	1.67 (0.97–2.90)	0.06
Heart rate (bpm)	0.95 (0.94–0.96)	**<0.001**	0.96 (0.95–0.98)	**<0.001**
Sum of differences	1.07 (1.05–1.09)	**<0.001**	1.05 (1.02–1.08)	**<0.001**

**ORs are according to reference categories Nulliparous or None. Singly nonsignificant predictors (Parity and Gestational Age, but not Yolk Sac) are not included in the multiple logistic regression model.*

gestational age by LMP, past history of spontaneous abortion, and parity were not.

A multiple logistic regression model was formed using these potential predictors. Although YSD yielded a *p*-value of 0.053 in simple logistic regression, it was included in the multiple logistic regression model. Maternal age, EHR, and proposed sum of differences were found to be significant in the multiple regression model (p=0.034, p<0.001, and p<0.001, respectively). The following odds ratios (ORs) and confidence intervals (CIs) for variables were found in the multiple logistic regression model: maternal age, OR=1.09, CI=1.01–1.17; indication for scan (none is reference)—spotting bleeding, OR=1.83, CI=0.62–5.31; heavy bleeding, OR=30.4, CI=3.68–251.25; pelvic pain only, OR=1.57, CI=0.48–5.17; vaginal bleeding and subchorionic hematoma combination, OR=2.93, CI=0.50–17.01 (OR for subchorionic hematoma cannot be calculated by the model); gestational age by gestational sac diameter, OR=0.99, CI=0.95–1.05; gestational age by CRL, OR=0.92, CI=0.84–1.01); YSD, OR=1.67, CI=0.97–2.90); heart rate, OR=0.96, CI=0.95–0.98; and proposed sum of differences, OR=1.05, CI=1.02–1.08.

Based on the abovementioned results, we propose a logistic regression model for predicting miscarriage. In order to keep the model simple, we constructed it with two predictors, namely heart rate and the proposed sum of differences. Other variables like indication for scan and maternal age were excluded because they made only minor contributions to the predictive ability of the final model.

Our proposed model is based on the following formula:

$$p=1/(1+\exp(-3.999-0.057\times\text{Sum of Differences}+0.048\times\text{EHR})),$$

where p is the probability of miscarriage for the embryo. The AUC (± (Standard error (SE)) of this model is calculated as 0.87±0.02, sensitivity as 0.509, and specificity as 0.975 with a cut-off=0.5. The prediction model's false positive rate is 0.025,

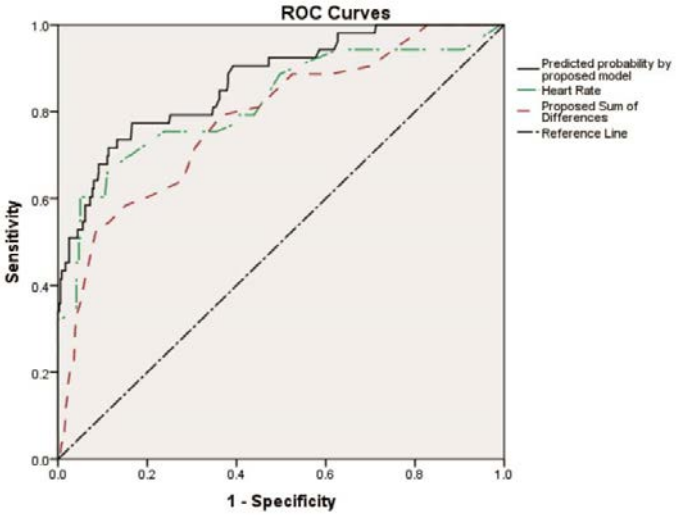

Figure 1: *ROC curves for the proposed model, heart rate, and proposed sum of differences*

Figure 2: *Decision tree for the prediction of risk of subsequent spontaneous miscarriage in live embryos in the first trimester*

and its false negative rate is 0.491. Figure 1 shows the ROC curve for the predictive ability of our proposed model.

Predictive abilities of EHR and proposed sum of differences were also evaluated by separate ROC curves. For EHR, the AUC was found to be 0.82, sensitivity 0.60, and specificity 0.95 with a cut-off value of 131. The proposed sum of differences had an AUC of 0.78, sensitivity of 0.53, and specificity of 0.91 with a cut-off of 21.2. Figure 1 shows the ROC curves for EHR and the proposed sum of differences.

To assist medical doctors in predicting miscarriage, we created a decision tree using predictors in our proposed model. The tree has a sensitivity of 0.34, specificity of 0.99, and overall classification rate of 0.90. The decision tree is shown in Figure 2.

DISCUSSION

The results from the present study demonstrate that the sum of differences between the gestational ages calculated using MGSD, CRL, and LMP via transabdominal USG performed between gestational weeks 6 and 10, combined with maternal symptoms of threatened miscarriage such as USG measures of EHR and YSD, can predict abortion that may develop. This possibility will become stronger with advanced maternal age and previous history of abortus.

More than 80% of abortions occur within the first 12 weeks of pregnancy; this rate drops rapidly from that point (11). At least half of these abortions are caused by chromosomal

abnormalities, and this incidence is inversely related to gestational age (12). The risk of spontaneous abortion increases with parity, as well as maternal and paternal ages. Although increasing maternal age (>35 years) probably has the greatest impact, several other factors (history of previous abortion, being underweight or overweight, tobacco, alcohol, low folate levels/intake, maternal medical conditions [e.g., diabetes]) carry an increased risk of sporadic first or early second trimester clinical abortion (13-16). Detection of early fetal cardiac activity in women with an advanced maternal age does not assure prognosis of pregnancy, while the possibility of predicted abortion is particularly high in those with low EHR, who require serial USG follow-up. In the current study, increasing maternal age demonstrated a trend toward an increased risk of subsequent miscarriage, as expected (OR, 1.09; 95% CI, 1.01–1.17). In our research, rate of the history of previous miscarriage was higher in the miscarriage group (41.5%) than in the normal outcome group (36.2%), although the difference was not statistically significant (p=0.453). In addition, the smoking rate was not significantly higher in the miscarriage group, because it was rather low in both study groups (4.8%); thus, further studies with larger series are required to determine the risk related with smoking.

Ten to fifteen percent of clinically recognized pregnancies end in first trimester or early second trimester losses (<20 weeks' gestational age). Following normal USG findings in the first trimester, the abortion rate was higher in pregnancies with a gestational age < 9 weeks (12.5%), a maternal age ≥ 35 years (15.5%) and vaginal bleeding (16.3%) (15). The rate of spontaneous abortion in our investigation was 12.8%. Abortion occurred in the first trimester in 43 of 53 (81%) pregnancies resulting in miscarriage, in accordance with the literature. Of 53 pregnant in women the miscarriage group, 11 (41.5%) had symptoms of threatened miscarried and 38 (71.6%) had abnormal USG findings (low CRL, EHR and MGSD, and high YSD), while 23 patients (43.3%) had both.

One in each four or five pregnant women may have spotting (27%) or heavy (8%) bleeding. Heavy bleeding in the first trimester, particularly when accompanied by pain, is associated with a higher risk of miscarriage. Spotting and light bleeding episodes do not point to a higher risk of miscarriage, especially if lasting only 1–2 days (17). In our study, spotting bleeding occurred in 60 (14.5%) patients, and 9 (15%) of them developed abortion. Thirteen (3.1%) patients experienced severe bleeding episodes, of whom 11 (84.6%) developed abortion. Sixty-two pregnant women (14.9%) were hospitalized due to symptoms threatening miscarriage, including bleeding and pelvic pain. Of a total of 415 pregnant women, the prediction model predicted 379 (91.3%) normal outcomes and 36 (8.7%) miscarriage cases. However, in the follow-up of the patients, it was found that abortion occurred in 26 of 379 patients in the normal outcome and 27 (75%) of 36 patients in the miscarriage group as predicted by the model. Among 140 pregnant women with symptoms threatening miscarriage, the model predicted 19 patients as belonging to the miscarriage group; of these patients, 18 (94.7%) actually developed miscarriage. In contrast, the model predicted that 121 patients would have a normal outcome even though they had symptoms of threatened miscarriage, while only 13 (10.7%) of these patients developed abortion. This indicates the contribution of the model in the prediction of subsequent abortions.

A decreased difference between the gestational sac and embryonic pole was first described by Robinson (1975) in the prediction of subsequent abortions in early live embryos (18). A more commonly used measurement of the gestational sac is MGSD. A small MGSD for CRL implies reduced amniotic and/or celomic fluid and is likely to reflect impaired placentation or fetal defect (19). In a study of 39 late first trimester abortions, Nazari et al. (1991) reported that small MSGD, small CRL, and a difference of MSGD–CRL less than 10.1 mm can predict abortus with 56% sensitivity (20). In addition, Dickey et al. (1992) reported 80% fetal loss when MSGD–CRL was less than 5 mm, 26.5% when the difference was between 5 and 7.9 mm, and 10.65% when the difference was greater than 8 mm; the authors emphasized importance of small gestational sac syndrome in early pregnancies (21). Similarly, Bromley et al. (1991) reported a rate of spontaneous abortion of 94% in cases with an MGSD–CRL difference of less than 5 mm and 8% in those with a difference greater than 5 mm (10). However, none of these three studies included fetal heart rate, yolk sac, or patient symptoms threatening miscarriage. Embryonic bradycardia of 85 beats per minute (bpm) or less is universally associated with impending miscarriage (8). However, a biometric parameter alone cannot be an absolute predictor of pregnancy outcome. Our clinical observations show that abortions occur not only in patients in whom a small gestational sac has been identified. Furthermore, patients who do not remember their LMP or have irregular cycles are also evaluated by clinicians and request information about the prognosis of their pregnancy. Again, although the superiority of transvaginal USG in the first trimester is generally recognized by clinicians, these patients' apprehension concerning transvaginal USG in the first trimester is undeniable. Therefore, we have created a new prediction model with the use of transabdominal USG in combination with patients' individual biometric parameters using transabdominal USG; this can also be used in pregnant women who do not remember their LMP.

In our study, abortion occurred in 61.5% of the patients with a fetal heart rate under 112 bpm and the cut-off value for the proposed sum of differences between the gestational ages was found to be 16.4. Meanwhile, the rate of miscarriage was 7.7% in pregnant women exhibiting a fetal heart rate higher than 112 bpm, and the cut-off value for the sum of differences between the gestational ages was found to be 40.5 in these patients. In conclusion, the risk of abortion was increased with decreasing fetal heart rate and increasing sum of difference between the gestational ages (Figure 1). The new proposed model created to predict this risk demonstrated the best ROC curve for predicting miscarriage (AUC of 0.87±0.02, sensitivity 0.75, and specificity 0.93).

There are several limitations to this study. First, genetic examination of aborted material to determine genetic abnormalities that caused abortion could not be carried out. Further studies including genetic research would establish the cause-and-effect relationship of abnormal USG findings. In addition, because pregnancies with abortus that developed after the detection of singleton live pregnancy were included, the proposed prediction model could be applied only in these patients. However, this study examined embryonic (which occurs at 6–9 weeks' GA) and fetal (which occurs at 10–20 weeks' GA) abortions, excluding preclinical or subclinical abortions (happening at or before weeks' GA), which are most commonly accompanied by genetic abnormalities.

CONCLUSIONS

We developed a new prediction model which indicates the likelihood of miscarriage; this method could be applicable to all pregnant women, irrespective of method of conception or history of menstrual cycles (in women with irregular menstrual cycles or uncertain LMP). We demonstrated that in women who present with a viable intrauterine pregnancy at the first scan, advancing maternal age, low EHR, and high proposed sum of differences in patients with threatened abortion indicate increased probability of subsequent spontaneous miscarriage. However, normal EHR, YSD between 95th and 5th percentile, and

proposed sum of differences less than 16.4 are associated with a lower rate of subsequent miscarriage, even in patients with spotting bleeding. There is no model that can exactly predict pregnancy outcomes. However, a high rate of prediction of patients with a poor prognosis could allow these patients to be informed and receive more intensive treatment. In contrast, pregnant women having a lower risk could be assured about there is no need for further workup until examination of fetal anatomy and aneuploidies at the 12th gestational week.

CONFLICT OF INTEREST: none.

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