The Egyptian Journal of Hospital Medicine (July 2025) Vol. 100, Page 4316-4322

Role Of 3D Doppler and Serum Level of Leptin as Biomarker in Threatened Miscarriage

Mohamed Fat'h Allah Abo-Elnasr[1], Emad Eldin Ali Solimana[2], Hossam El-Den Mahmod El-Ezzawy[2], Hanan Gomaa AbdelMaksoud[1], Abdelelbar Mohamed Sharaf*[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Menoufia, Egypt

[2]Department of Clinical Biochemistry and Molecular Diagnostics, National Liver Institute, Menoufia University, Menoufia, Egypt

***Corresponding author:** Abdelbar Abelmegeed Sharaf, **Mobile:** (+20) 01287885588, **E-mail:** abdelbar.abo7mza@gmail.com

ABSTRACT

Background: Leptin plays a critical role in early pregnancy stages, but its physiological function remains unclear.

Objective: To investigate the role of leptin serum level as a biomarker for early miscarriage and assess 3D-PDU findings in cases of early miscarriage.

Patients and Methods: This prospective case-control study was conducted between June 2023 and May 2024 in the Department of Obstetrics and Gynecology at Menoufia University and Meet Abo-Ghalib Central Hospital, involving 100 women aged 18-35 years. Participants were divided into two equal groups: a threatened abortion group and a control group. Serum leptin levels were measured by ELISA at 8 and 12 weeks. All patients underwent 3D-PDU examination at 8 and 12 weeks to assess vascularization index (VI), flow index (FI), and vascularization flow index (VFI).

Results: There was a significant increase in leptin levels from 8 to 12 weeks in both threatened and control groups, with significantly higher levels observed at 8 weeks in women with threatened miscarriage than controls. Leptin was negatively correlated with VI, FI, and VFI at around 8 weeks.

Conclusions: Serum leptin, along with 3D-PDU examination, is a reliable biomarker for predicting early pregnancy loss at 8 weeks.

Keywords: Threatened miscarriage; Leptin; 3D Doppler.

INTRODUCTION

Threatening miscarriage, also referred to as "threatened abortion," is any vaginal bleeding—with or without abdominal or pelvic discomfort and without cervical dilatation—that takes place before 20 weeks of pregnancy [(1)]. Preeclampsia (PE), preterm birth, intrauterine growth restriction (IUGR), preterm premature rupture of membranes (PROM), and placental abruption are among the negative pregnancy outcomes that it can cause, and it affects 15–20% of pregnancies [(2)].

Since leptin is produced in the fetoplacental unit and is involved in a number of reproductive processes, including the control of ovarian function, oocyte maturation, embryo development, and implantation, its role in pregnancy has been hypothesized. Additionally, a number of studies have shown that dysregulation of leptin metabolism and/or function may be linked to the pathophysiology of a number of pregnancy-related disorders, including IUGR, POS, PE, gestational DM, and recurrent miscarriages [(3)]. Alternatively, a prediction of the continuance of pregnancy in cases of early pregnancy loss might be made by estimating the blood level of the hormone leptin [(4)]. The levels of maternal plasma leptin increase during the 1st and 2nd trimesters of pregnancy, peak in the third trimester, and subsequently decrease to their pre-pregnancy levels before parturition [(5)].

Three vascular indices—VI, FI, and VFI—that may represent vascular density, blood flow, and tissue perfusion, respectively, are used in the Three-dimensional power Doppler ultrasound (3D-PDU) technique to allow for 1st trimester studies of placental vascularization [(6)]. During the 1st, 2nd and 3rd trimesters, preeclamptic patients showed a significant decline in placental VI, FI, and VFI. Before abnormalities in uterine artery PI were observed, there was a decline in 3D placental indices [(7)].

According to a prior study, women who experienced a poor pregnancy outcome due to defective placentation had a lower vascular flow index, which did not rise between weeks 8 and 12, than women who had a normal pregnancy. Women who experienced a poor pregnancy outcome had lower blood levels of leptin and higher levels of Ang1, which were associated with apparent underdeveloped placental vascular indices (PVIs) [(8)].

This study aimed to 1) investigate the role of leptin serum level as a biomarker for recurrent early miscarriage, thus finding an association that we can use in the prediction of these cases; and 2) the role of 3d Doppler findings in cases of recurrent early miscarriage.

PATIENTS AND METHODS

This prospective case control study recruited 100 pregnant women in their first trimester who attended outpatient clinics at the Department of Obstetrics and Gynecology at Menoufia University and Meet Abo-Ghalib Central Hospital over an 11-month period between June 2023 and May 2024.

Received: 30/04/2025
Accepted: 30/06/2025

Sample size: was determined using the mean serum leptin level that was previously predicted to be 27.33±9.705 ng/ml in group II at 9-12 weeks in pregnant women with a history of early pregnancy loss compared to the control 17.62±6.53 ng/ml [(9)]. The minimal sample size was 25 participants in each group using the following formula: considering 80% power and 95% CI.

$$n \geq \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2/r\right)}{\left(\mu_1 - \mu_2\right)^2}$$

(n=sample size, Z=Z statistic for the level of confidence of 95%, (Z=1.96), β=the critical value of the normal distribution at β (e.g., for a power of 80%), σ2 =population variance, μ= means).

Therefore, a total of 100 participants were required for this study, which was divided into 2 groups: 1) a case group of 50 pregnant women having threatened abortion, and 2) a control group of 50 pregnant women with normal pregnancies who were matched for age.

Patients' criteria

Regrading threatened group, inclusion criteria were pregnant women between the ages of 18-35 who had threatened abortion 8 weeks and 12 weeks gestational age (GA), which was determined by taking the first day of their most recent menstrual cycle, followed by 3 regular menstrual cycles, and comparing it with US measurements; having a singleton viable fetus and a visible gestational sac with intact heart beats, or presence of fetal bone; also include pregnant women with assisted reproductive technique (ART).

We excluded pregnant women who had a history of medical diseases such as Diabetes or thyroid illness, gynecological conditions such as fibroid, and uterine deformities such as spectate or hypoplastic uterus.

Methods

All study participants underwent a thorough history that included age, personal medical history, any reported problems, obstetric history, menstrual history, prior medical and surgical history, and family history.

Additionally, a general physical examination was conducted involving the evaluation of vital signs (heart rate (HR), blood pressure, temperature) and anthropometric measurement (weight, height, and body mass index (BMI, kg/m^2).

Leptin immunoassay

Maternal blood samples were obtained at 8 weeks and 12 weeks of pregnancy under aseptic conditions. 5 ml blood was enough to be centrifuged and get about the (2-3 ml) serum. Serum-separating tubes (yellow-topped) were utilized to enhance the centrifugation process. All specimens of serum were divided into 2 parts to minimize the possibility of any fault occurring as we take it at a specific time, and it would be difficult to rearrange or retake the specimen again at the exact time from the woman.

Circulating levels of leptin were measured using Leptin Human ELISA Kit Instruction Catalogue No.: DEIA1560 (Creative Diagnostics); the minimum detectable value was 0.2 n/ml. The intra- and inter-assay coefficients of variation (CV) of leptin were 4% and 6%, respectively.

Three-dimensional power Doppler ultrasound examination

All Doppler studies were performed at 8 and 12 weeks using an ultrasound machine utilizing a wideband convex ultra-right volumetric probe (2-8 MHz) with an insonation angle of 146° (Voluson S10Expert Women's Health US, GE Health Care, USA). Every patient was examined while lying down with her abdomen visible. 3D power Doppler angiography was used to determine the volume of the whole placenta and subplacental tissue. As much as feasible, the embryo was not included in the power Doppler window, which was positioned above the placenta and subplacental region. All tests used the same power Doppler characteristics: a 50Hz wall motion filter, a 600Hz pulse repetition frequency, a color gain of -3.4, and standard color quality. The placental size to be photographed was taken into consideration while choosing a sweeping angle, which ranged from 35° to 90°.

VOCAL (Virtual Organ Computer-aided Analysis) was used to save the volumes for further analysis. The multiplanar system was used to find the placenta by exploring the three planes of the placental/subplacental volume that was acquired. Using the same parameters as for placental volume measurement, a broad vascular subplacental region around the placenta was delineated in order to assess subplacental vascularization.

While the results from the subplacental area were thought to indicate uteroplacental circulation, the intraplacental area's results were thought to show intervillous circulation. Images in three dimensions were produced using the glass body technique. The VOCAL software automatically determined the three 3D power Doppler indices, VI, FI, and VFI, as well as the placenta's volume (PV) based on the uteroplacental and intervillous circulations.

Ethical consideration

The Research Ethics Committee of Menoufia University's Faculty of Medicine gave its clearance to the study (ethical approval code: 6/2023OBSGN1). Prior to their registration in the trial, all individuals provided

written informed consent. Furthermore, any participant was free to leave the research at any moment without having an impact on their course of therapy because participation was entirely voluntary. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis

SPSS version 25.0 was used to analyze the data. The X^2-test or Fisher's exact test for tiny, predicted cell frequencies were used to compare categorical data, which were reported as absolute frequency (N) and percentage (%). Shapiro-Wilk's test was first used to check for normality in continuous data. The mean ± (SD) of the normally distributed data were displayed.

Two independent groups were compared using an independent sample t-test, and paired data at 8 and 12 weeks with a normal distribution were compared using paired t-tests. The relationship between leptin levels and 3D-PDU indicators was examined using a Pearson correlation coefficient test. The significance threshold was established at a P value of less than 0.05.

RESULTS

The mean age of the participants in the threatened group was 27.12±5.35 years, and the control group was 26.04±4.04 years. Nevertheless, there was no statistically significant difference between the 2 groups. Also, BMI, gravidity, parity, and HR did not show statistically significant difference between the threatened and control groups (*P*>0.05 for each).

Regarding the distribution of history of previous abortions, there was a statistically significant higher incidence of prior one-time abortion, 42(84%), among the threatened group compared to no one in the control group (Table 1).

Table (1): Comparison of demographic and clinical characteristics between the studied groups

Variables	**Threatened group (N=50)**	**Control group (N=50)**	***P*-value**
Age (years)	27.12±5.35	26.04±4.04	0.25
BMI (Kg/m^2)	24.18±3.4	23.94±3.28	0.72
Gravidity	2.92±1.61	2.8±1.62	0.71
Parity	1.3±1.07	1.24±1.07	0.77
HR (beat/ min)	85.6±7.56	83.02±8.85	0.12
History of previous abortion, n (%) 0 1 2 3 4	 0(0%) 42(84%) 6(12%) 1(2%) 1(2%)	 50(100%) 0(0%) 0(0%) 0(0%) 0(0%)	**<0.001***
Vaginal bleeding, n (%) Spotting Mild Moderate Nil	 29 (58%) 16 (32%) 5 (10%) 0 (0%)	 6 (12%) 0 (0%) 0 (0%) 44 (88%)	**<0.001***
Uterine cramps, n (%) Nil Mild Moderate	 11 (22%) 30 (60%) 9 (18%)	 40 (80%) 10 (20%) 0 (0%)	**<0.001***

*:Significant.

There was a statistically significant increase in leptin from 8 to 12 weeks in both the threatened and control groups, as shown in table 2. Additionally, the mean leptin levels at 8 weeks in threatened patients were statistically significant elevated compared to those in the control group. However, there was no statistically significant difference between the threatened group and the control group at 12 weeks.

Table (2): Comparison of leptin at 8 and 12 weeks between the studied groups

Leptin (ng/mL)	**Threatened group (N=50)**	**Control group (N=50)**	**MD**	**P-value[b]**
At 8 weeks	15.05± 3.17	12.81±3.39	2.24±0.87	**0.01***
At 12 weeks	26.86±2.05	26.21±4.24	0.65±0.01	0.72
MD	-11.81± 2.91	-13.40±3.93		
P-value [a]	**<0.001***	**<0.001***		

MD: Mean difference; [a]: Independent t-test, [b]: Paired t-test; *:Significant.

Table 3 illustrates the placental volume and PVIs, including VI, FI, and VFI, at 8- and 12-weeks using 3D PDU for both the threatened and control groups. There was a significant increase in the placental volume, VI, FI, and VFI, from 8 to 12 weeks in both groups. Additionally, statistically significant lower mean placental volume, VI, FI, and VFI levels were observed in threatened patients compared to the control group at 8- and 12-weeks GA.

Table (3): Comparison of placental volume and PVIs at 8 and 12 weeks between the studied groups

Variables		**Threatened group (N=50)**	**Control group (N=50)**	***P*-value[a]**
Placental volume (mm^3)	**At 8 weeks**	30.56±4.51	35.16± 2.05	**<0.001***
	At 12 weeks	38.47±5.68	87.47±5.68	**<0.001***
	***P*-value[b]**	**<0.001***	**<0.001***	
VI	**At 8 weeks**	1.07±0.02	1.88±0.03	**<0.001***
	At 12 weeks	1.66±0.28	11.35±0.11	**<0.001***
	***P*-value[b]**	**<0.001***	**<0.001***	
FI	**At 8 weeks**	10.9±0.46	16.29±0.28	**<0.001***
	At 12 weeks	19.36±0.44	28.32±2.56	**<0.001***
	***P*-value[b]**	**<0.001***	**<0.001***	
VFI	**At 8 weeks**	0.55±0.03	0.85±0.02	**<0.001***
	At 12 weeks	2.90±0.32	4.56±0.17	**<0.001***
	***P*-value[b]**	**<0.001***	**<0.001***	

VI=vascularization index; VFI=vascularization flow index; FI=flow index.
[a]:Independent t-test; [b]:Paired t-test; *:Significant.

There was a –ve significant correlation between leptin and VI, FI, and VFI at 8 weeks, although no correlation was found with placental volume (**Table 4**). However, no significant correlation was observed between leptin and ultrasound findings at 12 weeks.

Table (4): Correlation between leptin and ultrasound findings at 8 and 12 weeks

Variables	**Leptin (ng/mL)**			
	At 8 weeks		**At 12 weeks**	
	r	***P*-value**	**r**	***P*-value**
Placental volume (mm3)	-0.137	0.173	-0.055	0.588
VI	**-0.256**	**0.010***	-0.078	0.442
FI	**-0.249**	**0.013***	-0.044	0.661
VFI	**-0.275**	**0.006***	0.027	0.791

r: Pearson correlation coefficient; *: Significant.

As shown in **table 5**, women with threatened abortion had a statistically significant higher frequency of the occurrence of subchorionic space than the control group. There was no statistically significant difference regarding FHR between threatened group and control group. There was a statistically significant high rate of patients who lost pregnancy, a difference between the threatened group and the control group. A higher statistically significant pregnancy loss rate was observed between the threatened group compared to the control group.

Table (5): Ultrasound findings and the distribution of pregnancy loss distribution between the studied groups.

Variables	**Threatened group (N=50)**	**Control group (N=50)**	***P*-value**
Subchorionic hematoma, n (%) No Yes	 40 (80%) 10 (20%)	 50 (100%) 0 (0%)	**<0.001***
Fetal heart rate (FHR) (beat/ min)	137.08±12.84	133.28±11.81	0.126
Pregnancy loss, n (%)	10(20%)	2(4%)	**0.03***

*: Significant.

DISCUSSION

In this prospective case control study, we investigated the role of leptin serum level as a biomarker for recurrent early miscarriage, thus finding an association that we can use in the prediction of these cases, additionally, we examined the role of 3D-PDU findings in cases of recurrent early miscarriage.

Age and BMI did not significantly differ between the 2 groups in this research. This finding aligns with **Bhoil *et al.*'s** [7] study, which found the mean age of women with threatened miscarriage was 27.45 ± 3.27 years and 26.72 ± 4.83 years in the control group, with no significant difference between the two groups. Also, they found no significant BMI difference between women at risk of miscarriage and the control group.

In contrast, **Leijnse *et al.*** [10] reported that BMI was significantly higher by~13% in women with adverse pregnancy outcomes compared to uneventful pregnancy outcomes. The variations in findings among these studies could be attributed to differences in ethnicity, type of methodologies, and sample size.

In the current study, a significantly higher rate of one-time previous abortion was found among women who had threatened abortion compared to the control group, indicating an association between threatened miscarriage and an elevated incidence of adverse pregnancy outcomes. This result aligns with earlier research carried out by **Abd El-Raheem *et al.*** [1] **and Zakaria *et al.*** [11]**,** which reported a statistically significant higher incidence of one-time previous abortions in the threatened group (25% and 28.9%, respectively) compared to normal pregnant women (0% and 10.5%, respectively). Also, a recent study found 84.4% had one-time and more previous abortions among the threatened abortion group (risk ratio 0.95, 95% confidence interval 0.82–1.11) [12]. Conversely, another study revealed no statistically significant difference regarding the distribution of previous abortions between the threatened and control groups [13].

In present study, women with threatened abortions had a significantly higher incidence of mild to moderate bleeding compared to the control group. This is in line with a prior study that found that 80% of individuals who were at risk of miscarriage experienced minor vaginal bleeding [14]. Also, **Poulose *et al.*** [15] investigated the association between the quantity of vaginal bleeding and the risk of miscarriage, and their results showed that the risk of miscarriage is 2.6 times higher for moderate and severe vaginal bleeding than for light hemorrhage. Nevertheless, 75% of the pregnancies remained to be viable despite a history of severe hemorrhage.

According to a prior study, leptin levels peak around 28 weeks of pregnancy and then remain comparatively constant until a notable drop in pre-pregnancy levels occurs within the first 24 hours after giving birth, indicating a clear functional role for leptin during pregnancy [16].

Furthermore, **Wendremaire *et al.*** [17] looked into the possibility of leptin causing contractions of myometrial cells in a validated co-culture paradigm and discovered when leptin without lipopolysaccharide (LPS) was used to activate myometrial cells co-cultured with macrophages, they found that a high dose of leptin (50 ng/mL) caused spontaneous myocyte contraction. Moreover, the study showed that when myometrial cells were cultivated with macrophages, leptin might prevent the contractions caused by LPS. The addition of leptin at a dosage of 5 ng/mL inhibited the increase in spontaneous contractions caused by LPS stimulation.

The current study demonstrated that women who experienced threatened abortion had significant higher levels of leptin compared to those with normal pregnancies at 8 weeks. There was also a significant increase in leptin levels from 8 to 12 weeks in both groups, despite 12 weeks, the difference between the two groups being statistically insignificant. Furthermore, impending miscarriage is a clinical illness with a variety of reasons; the infections present in the community may vary. Therefore, in situations of early pregnancy loss, predicting the continuation of the pregnancy might be done by assessing the blood level of the hormone leptin.

Similarly, a prior study by **Mutalib and Yaqoub** [14] discovered that pregnant women with a history of recurrent early pregnancy loss had significant higher levels of leptin hormone at weeks 5-8 and 10-12 (12.53±3.62 and 18.38±5.36 pg/ml, respectively) than the control group (6.26±3.31 and 7.23±3.94 pg/ml) during the same time period. Notably, the study also showed that the mean level of leptin hormone decreased significantly between the 5-8th and 10-12th weeks.

A different study of pregnant women in the first trimester also found that the mean serum leptin level was significantly higher in those with a history of early pregnancy loss than in the control group (12.75±2.147 ng/ml and 17.62±6.53 ng/ml, respectively) from 19.477±7.501 ng/ml in the first sample at 5-8 weeks and 24.183±9.705 ng/ml in the second sample at 9-12 weeks. This difference was statistically significant, suggesting that hyperleptinemia was linked to early pregnancy loss [18].

In a previous study, women who subsequently miscarried had significantly lower plasma leptin concentrations on both weeks 5-6 (13.34±2.1 ng/ml) and 7-8 (13.71±2.4 ng/ml) of pregnancy, than women who subsequently had a term birth (22.04±2.43 ng/ml week 5-6, 24.76±3.66 ng/ml week 7-8), indicating that miscarriage prevention may be aided by the noticeably decreased leptin levels in women who later miscarried [19].

The rs7799039 G/A in leptin and miR-27a polymorphisms is linked to an increased vulnerability to recurrent pregnancy loss (RPL), according to research examining the significance of these polymorphisms in the development of idiopathic RPL [20]. Additionally, **Wang *et al.*** [20] found that polymorphisms in leptin rs7799039 G/A and MiRNA-27a rs895819 A/G raised the incidence of recurrent spontaneous abortion (Exp (B)=2.732, 95% CI=1.625~4.596; Exp (B)=4.081, 95% CI=1.817~9.164).

Observational research, on the other hand, discovered no appreciable variations in blood leptin levels between women who had a threatened miscarriage and a subsequent miscarriage and those who had a threatened miscarriage and a term delivery [21]. In the first trimester, early screening for placental vascular diseases may lower morbidity and death rates for both mothers and fetuses [22].

The 3DPD technique could be reliable for measuring uteroplacental vascularization and understanding uteroplacental physio-pathological mechanisms. The present study found a significant reduction in placental volume and PVIs (VI, FI, and VFI) among women who experienced threatened abortion compared to those with normal pregnancies at 8 weeks. Also, there was a highly statistically significant lower placental volume and PVIs in the threatened group at 12 weeks than in the control group, suggesting that there was higher placental resistance and significantly lower placental blood perfusion in the threatened abortion group compared to the control group. The placental blood perfusion indexes of VI, FI, and VFI increased with the increase in GA, indicating that the vascular network and blood flow in the placenta also increased with the rise in GA [23].

According to the findings of **Leijnse *et al.*** [10]**,** in women with uneventful pregnancies, VI and vascular FI rose by about 50% between 8 and 12 weeks, resulting in a roughly 50% higher VI at 12 weeks than in those with unfavorable pregnancy outcomes. Additionally, indices and placental volumes were considerably lower for women with unfavorable pregnancy outcomes at all time periods evaluated, and they did not rise between 8 and 12 weeks.

Likewise, another study found that women who had a poor pregnancy result had substantially lower indices and placental volumes at all time periods examined than those who had a normal pregnancy outcome, however these indices did not rise between 8 and 12 weeks [24].

A study conducted on an uncomplicated pregnancy, the mean VI was observed to increase from 8.66±12.04 to 18.00±15.39 and 15.34±13.89 at 7, 8, and 10±6 weeks, respectively. The mean FI also exhibited a rise from 68.83+43.61 to 94.32±15.39 and 109.22±33.87. Furthermore, the VFI showed an increase from 9.52±13.86 to 18.54±17.11 and 20.59±22.97 [25].

On the other hand, a study carried out by **Sweed *et al.*** [26] demonstrated that the following cutoff values could be used to predict poor pregnancy outcomes: VI≤3.22, FI≤17.73, and VFI≤0.5 for preeclampsia (PE), and VI ≤ 4.12, FI ≤ 15.93, and VI≤ 0.3 for FGR. The study suggests that evaluating placental bed vasculature with 3D power Doppler in the first trimester can be a useful tool in predicting poor pregnancy outcomes.

The threatened miscarriage group and the control group did not vary statistically significantly in FHR, according to the current study. This result is still unknown since it might be because the embryonic heart rate is within the typical range for pregnancy. For individuals with a first-trimester threatening abortion, the optimal cutoff point for predicting pregnancy loss was an FHR<120 beats per minute [27].

Conversely, it is notable that contradicting results have been reported by other investigations. According to **Lotfy *et al.*** [13] the mean FHR women who experienced symptoms suggestive of a threatening miscarriage were significantly lower (131.1±23.75 beat/min) than those who had straightforward pregnancies (150.9±16.49 11 beat/min).

Romero-Gutiérrez *et al.* [19] evaluated the FHR and Doppler velocimetry and found one patient with an FHR less than 100 beats per minute who later had an abortion. The authors examined the FHR and discovered that bradycardia was related with a higher probability of spontaneous abortion.

This study reported a significant higher incidence of patients who lost pregnancy in a threatened group (20%) compared to the control group (4%). This result aligns with another study who found that 22.5% of those with threatened abortion had an abortion before 20 weeks, while 77.5% continued their pregnancy past 20 weeks, with a significant difference between threatened miscarriage and the control group [28].

To our knowledge, this study has many strengths, including a comparative analysis of leptin levels, placental volume, and PVIs between women experiencing threatened miscarriage and those with normal pregnancies at 8 and 12 weeks, as well as assess the correlation between leptin as a biomarker in predicting threatened miscarriage and 3D Doppler findings at 8 and 12 weeks.

Limitations: Including the small sample size and being carried out in a single institution. Our study focused on predicting threatened miscarriage, but long-term adverse perinatal outcomes were not assessed. Moreover, our study didn't determine the timing of bleeding. Another limitation of our study is the rarity of assessing the relationship between leptin levels and adverse pregnancy

outcomes in patients with the subchorionic space and non-subchorionic space groups.

CONCLUSION

Serum leptin, along with 3D-PDU examination, is a reliable biomarker for predicting early pregnancy loss at 8 weeks.

No funding.
No conflict of interest.

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