



Original article

Midluteal Assessment of Uterine Artery Doppler and Serum Progesterone Level in Women with Unexplained Recurrent Miscarriage

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Abstract

Objective: To investigate the blood flow and progesterone levels in non-pregnant women with a history of unexplained recurrent pregnancy loss (RPL) in comparison to normal fertile women. **Patients and methods:** This case control study was done at Department of Obstetrics and Gynecology in Beni-Suef University from October 2020 to April 2021. Cases with history of unexplained RPL (n = 55), and controls with no history of miscarriage and at least one term delivery (n = 55). Serum progesterone measurement and transvaginal uterine artery Doppler were conducted to all participants in the midluteal phase to assess the uterine artery pulsatility index (PI), resistance index (RI) and serum progesterone

level. **Results:** Uterine artery PI and RI were significantly higher in the study group ($p < 0.001$). On the other hand, there was no significant difference in serum progesterone level between the two groups ($p=0.855$). The cut-off value of uterine artery RI > 0.85 and the cut-off value of uterine artery PI > 2.3 were significantly associated with unexplained RPL. **Conclusions:** This study concluded that serum progesterone had no role in prediction of unexplained RPL. Uterine artery PI and RI had a role in prediction of unexplained abortion, but the PI is better than RI in the prediction of unexplained RPL.

1. Introduction:

Abortion is described as the loss of a pregnancy before 20 weeks of pregnancy or with a foetal weight of less than 500 grams. Both ectopic pregnancies and molar pregnancies, according to the majority of researchers, should not be included in the definition [1].

As unpleasant disorder, recurrent miscarriage (RM) affects approximately one percent of couples who are trying to get pregnant. It can be extremely disappointing for both clinicians and patients when, despite extensive workup, no identifiable underlying disease is discovered in at least half of all couples with this condition [2].

There is no agreement on the number of miscarriages that must occur before a woman is considered to have recurrent miscarriage. The Royal College of Obstetricians and Gynecologists (RCOG) in the United Kingdom defines recurrent miscarriage (RM) as “the loss of three or more successive pregnancies”. In addition, the Austrian and Swiss Societies of Gynecology and Obstetrics define RM as three or more consecutive losses [3]. However, the American Society for Reproductive Medicine defines recurrent abortion as two or more failed clinical pregnancies with exclusion of biochemical pregnancies but requiring only two losses in order to be considered RM [4].

Uterine malformations, antiphospholipid syndrome, hormonal and metabolic problems, and chromosomal abnormalities are all well-documented causes of recurrent miscarriage (RM). A number of other etiologies have been proposed, but they are still regarded problematic, including chronic endometritis, hereditary thrombophilia, luteal phase insufficiency, and high sperm DNA fragmentation levels [5].

The use of scientifically validated interventions, such as surgical correction of uterine abnormalities or antiphospholipid syndrome treatment with aspirin and heparin, has significantly improved the outcomes for couples who have experienced recurrent pregnancy loss over the years. However, about half of the cases remain unexplained, and they are treated empirically with progesterone supplements, anticoagulation, and/or immunomodulatory therapies [6].

It has been reported in the literature that ultrasonography and biochemical indicators such as serum progesterone level, either alone or in combination, can be used to predict miscarriage, which is particularly relevant in cases of RM [7].

Progesterone levels in the blood have been proposed as a predictive biochemical marker of recurrent miscarriage in a number of scientific studies. An aberrant luteal phase is related with serum progesterone levels larger than 10 ng/mL in the mid-luteal phase only in a small number of cases. Although low serum progesterone levels (less than 12 ng/ml) have been linked to an increased risk of miscarriage, there is no evidence to support this [8].

Because of the pulsatile nature of progesterone release, progesterone levels might fluctuate during measurements, making interpretation of progesterone levels more difficult in some cases [9].

Uterine artery doppler has been widely used in the field of recurrent pregnancy loss (RPL) in recent decades because it is an effective, reliable, and noninvasive method of assessing endometrial receptivity that is noninvasive and does not require any intervention. Many studies have shown that optimal uterine perfusion, while retaining appropriate endometrial receptivity, is essential for successful embryo implantation and growth [10].

In addition to serving as the primary source of uterine blood flow, the uterine artery is also critical in the maintenance of proper uterine perfusion throughout pregnancy. Numerous investigations have demonstrated that the resistance to uterine artery blood flow is higher in RPL patients than in the general population [11].

As a result of these findings, researchers have discovered that RPL patients with antiphospholipid syndrome (APS), Müllerian uterine abnormalities, or an undetermined origin have much higher resistance to the flow of uterine artery blood when compared to those in a control group. Others said that insufficient uterine arterial blood circulation could play a crucial role in the aetiology of RPL [12].

2. Aim of the work:

To investigate the blood flow and progesterone levels in non-pregnant women with a history of unexplained recurrent pregnancy loss (RPL) in comparison to normal fertile women.

3. Subjects and Methods:

This case-control study was done in obstetrics and gynecology department in

Beni-Suef University Hospital from October 2020 to April 2021 and was applied on 110 non pregnant women.

Subjects:

Group I (Cases Group): Included 55 women with recurrent pregnancy loss .

Group II (Control Group): Included 55 healthy fertile non-pregnant women (20-35 years) with no history of previous miscarriage and had at least one child born at term. They did not receive any hormonal contraception or use IUCD at the time of study with the same exclusion criteria as the study group.

Cases were selected according to the following inclusion/exclusion criteria:

- ❖ **Inclusion criteria:** Women with age: 20-35 years, with history of recurrent miscarriage (defined as ≥ 3 previous miscarriages at < 20 weeks' gestation) fathered by the same partner, with regular menstrual cycles at least for the last 3 months, and with no hormonal contraception or intrauterine devices were used at the time of study were eligible to be selected in the study.
- ❖ **Exclusion criteria:** Women with one or more of the following conditions as

diabetes mellitus, hypertension, cardiac or renal disease, abnormal coagulation profile, thyroid disorders, hyperprolactinemia, luteal phase deficiency, documented uterine anomalies, positive one or both markers of antiphospholipid antibody syndrome, positive antinuclear antibodies, cervical incompetence, smoking, family history of chromosomal abnormalities (e.g. trisomy or Turner's disease), history of consanguinity, and failure to obtain consent were excluded from the study.

Methods:

All women were subjected to the following:

Full history taking:

- ❖ **Personal history:** their names, ages, addresses, occupations, special habits, and history of consanguinity.
- ❖ **Menstrual history:** asking about regularity of cycles, frequency, duration and amount of bleeding of each cycle, and date of the last menstrual period.
- ❖ **Obstetric history:** asking about parity and method of previous deliveries, time at which previous abortions had been occurred and whether they had been followed by surgical evacuation or not, and ask about date of the last delivery or abortion.

- ❖ **Past history:** past history of systemic diseases such as diabetes mellitus, hypertension, renal disease, past history of infants with chromosomal abnormalities such as trisomy 21, and past history of thyroid troubles.

Thorough clinical examination:

- ❖ **General examination:** Signs of thyroid disease, autoimmune disease, cardiovascular disease ,etc.
- ❖ **Breast examination:** for swelling or nipple discharge.
- ❖ **Abdominal examination:** Inspection, palpation and percussion were done to exclude any detectable pathologic lesions e.g. splenomegaly and hepatomegaly.
- ❖ **Pelvic examination:** to assess uterine size and the presence or absence of adnexal masses.

Laboratory investigations:

- Random blood sugar was done for the study group and the control group.
- IgG and IgM titre for anti-cardiolipin antibodies, Lupus anticoagulant were done for the study group.
- Measurement of TSH for the study group.
- Evaluation of serum progesterone level: was done during the mid-luteal phase (Day 21 of regular menstrual cycle) in

women of the study group and the control group.

Ultrasonographic evaluation:

All examinations were performed using MINDRAY DC N2 ultrasound equipment equipped with 6.5 MHz transvaginal transducer with pulsed color Doppler and by the same examiner in the mid-luteal phase of menstrual cycle for all women of the study and control group.

- Pelvic ultrasound examination with abdominal probe was done to exclude the presence of large adnexal or pelvic masses.
- Transvaginal ultrasound examination was done to exclude any uterine or adnexal abnormalities.
- Transvaginal bilateral uterine artery Color Doppler assessment of Pulsatility index (PI) and Resistance index (RI) was done. A pulsed colour Doppler examination of the right uterine artery (located at the lateral border of the uterine isthmus) was performed first, followed by an evaluation of the left uterine artery. Because there was no discernible difference between the right and left sides, it appeared possible to confirm that the most accurate way to interpret Doppler data for uterine arteries would be to utilise the mean PI and RI of both sides combined, as previously

reported [13]. So, the average pulsatility index (PI) and resistance index (RI) of the bilateral uterine arteries were calculated.

Study outcome

Primary outcomes:

- Evaluation of uterine artery blood flow during the mid-luteal phase in women with recurrent unexplained abortion and comparing them to normal fertile controls.
- Evaluation of serum progesterone level during the mid-luteal phase in women with recurrent unexplained abortion and comparing them to normal fertile controls.

Secondary outcomes:

- Studying the effect of age on recurrent abortion.
- Studying the effect of obesity on recurrent abortion.
- Correlation between uterine artery Doppler parameters and mid-luteal serum progesterone level, age and BMI.

Statistical analysis:

Analysis of data was performed using SPSS v. 25. The mean and standard deviation of quantitative variables served as the basis for their description (SD). Nouns and percentages were used to describe qualitative variables in the quantitative data

collection (percent). Data was explored for normality using Shapiro/ Kolmogorov tests of normality. Data was normally distributed. Comparison between the scale variables of the two groups was assessed by the independent t-test. Comparison between both groups regarding categorical variables was conducted by Chi-Squared test. Receiver operating characteristic curve was used to assess the optimal cut off point of uterine artery RI and PI for prediction of unexplained recurrent miscarriage. Pearson correlation was conducted to assess the linear correlation between uterine arteries'

PI and RI and patient's age, BMI and progesterone level. Results were evaluated for significance using a P-value, which was divided into two categories: non-significant when the P-value was greater than 0.05 and significant when the P-value was less than or equal to 0.01.

Ethical consideration:

The current study was conducted approval by the research ethics committee of faculty of medicine in Beni-Suef University. No one obliged to participate in this study. Informed consent was obtained from all participants.

4. Results:

Table (1) Baseline characteristics of the studied groups:

Characteristics	Cases (no=55)	Controls (no=55)	P-value
Age (mean±SD)	27.8±4.7	28.1±4.3	0.721
BMI (mean±SD)	25.1±3.2	24.6±2.8	0.352

Table (1) showed that there was no statistically significant difference between cases and controls regarding their age and BMI (both groups were well matched) (P-value > 0.05).

Table (2) Progesterone level in cases and controls:

item (mean±SD)	Cases (no=55)	Controls (no=55)	P-value
Progesterone level	11.1±3	10.9±3.5	0.855

Table (2) showed that there was no statistically significant difference between cases and controls regarding their progesterone level (as cases group had unexplained recurrent abortion) (P-value > 0.05).

Table (3) Comparison between cases and controls regarding uterine artery Doppler parameters:

Uterine artery	Cases (no=55)	Controls (no=55)	P-value
PI (mean±SD)	2.59±0.53	1.85±0.33	<0.001*
RI (mean±SD)	0.91±0.11	0.81±0.09	<0.001*

Table (3) showed that there was a significant higher uterine artery PI and RI among cases than controls (P-value<0.001).

Table (4): Comparison between uterine artery PI and RI regarding their role in prediction of unexplained abortion:

Items	PI	RI
P-value	<0.001*	<0.001*
Cut off	>2.3	>0.85
AUC	0.875	0.765
Sensitivity (95%CI)	72.73(59.0 - 83.9)	80.00(67.0 - 89.6)
Specificity (95%CI)	94.55(84.9 - 98.9)	70.91(57.1 - 82.4)
PPV (95%CI)	93.0(81.4 - 97.6)	73.3(64.1 - 80.9)
NPV (95%CI)	77.6(69.1 - 84.3)	78.0(67.1 - 86.1)

Table (4) showed that the uterine artery PI and RI have a significant role in prediction of unexplained recurrent abortion (P-value <0.001).

At a cut off 2.3 or more of uterine artery PI, it can significantly predict the unexplained recurrent abortion with 72.73% sensitivity, 94.55% specificity, 93.0% PPV and 77.6% NPV.

At a cut off 0.85 or more of uterine artery RI, it can significantly predict the unexplained recurrent abortion with 80.0% sensitivity, 70.91% specificity, 73.3% PPV and 78.0% NPV.

Table (5): Correlation between uterine artery Doppler parameters and patients' age, BMI and progesterone level:

Parameters		Uterine PI	Uterine RI
Progesterone	R	0.196	0.045
	P-value	0.153	0.745
Age	R	-0.079	0.016
	P-value	0.569	0.909
BMI	R	-0.002	0.177
	P-value	0.990	0.196

Table (5) showed that there was no statistically significant linear correlation between the uterine arteries' PI and RI and patient's age, BMI and progesterone level (P-value >0.05).

5. Discussion:

In the current study it was found that there was statistically insignificant difference between both groups as regards age (P-value =0.721) (table 1).

This agreed with Elsayah et al.,[14] and Garhy et al.,[13] who did not find any significant difference between women with unexplained recurrent abortion and their controls regarding their age.

In contrast, Abdel Wahab et al.,[15] found a significantly higher age in cases with

recurrent miscarriage than the control group (28.6 ± 4.6 years and 26.2 ± 4.7 years,

respectively) (P= 0.02). This was due to a decrease in endometrial receptivity linked with a decrease in uterine perfusion as a result of increased maternal age, which resulted in a fall in the implantation rate.

In the current study, it was found that there was no statistically significant difference between the BMI of women in the RPL group and the control group P= 0.352 (table 1).

Sugiura-Ogasawara [16] found that obesity might increase the danger of spontaneous miscarriage. Body mass index more than 30 kg/m² increases the risk of abortion with odds ratio 1.7-3.5 in patients with early recurrent abortion.

In addition, King and Casanueva [17] and Lashen et al.,[18] reported that obese women have a 20 percent higher chance of spontaneous abortion than women with a normal BMI.

Because all women in this study were selected with normal BMI, we can't document the controversy between our results and the previous studies.

In our study there was statistically insignificant difference between cases and controls regarding their mid-luteal progesterone level with P value =0.855 (table 2).

This agreed with Yan et al., [19] who reported that There was insignificant difference in the mid-luteal serum progesterone levels between the cases of abortion group and the live birth group (13.36± 1.006 ng/ml and 13.3± 0.754ng/ml, respectively). Therefore, they asserted that measuring mid-luteal serum progesterone in women who have experienced unexplained recurrent loss does not predict the fate of a subsequent pregnancy. This supported the findings of a previous study by Ogasawara et al.,[20], which discovered that decreased progesterone production by the corpus luteum is unlikely to be a substantial contributing factor to recurrent miscarriage.

Also, Elsayah et al., [14] found that serum progesterone level was insignificantly higher in control group (12.87±2.47) than in case group (12.66±3.17).

In contrast, Garhy et al., [13] reported that serum progesterone level of women in the control group (14.3 ± 2.4) was significantly

higher than that in the RPL group (14.0 ± 2.7) with P-value =0.002.

In the current study, the mean PI and RI of uterine artery were significantly higher in the RPL group compared to the control group (2.59 ± 0.53 , 1.85 ± 0.33 , 0.91 ± 0.11 and 0.81 ± 0.09 , respectively) with P value < 0.001 (table 3).

Our study agreed with Ferreira et al., [21] who found that women with a history of repeated pregnancy loss had a considerably greater uterine artery PI than those in the control group (2.71 ± 0.54 and 2.30 ± 0.44 , respectively) with P < 0.001. In addition, Abdel Wahab and colleagues [15] concluded nearly equal results with their explanation evidenced by higher uterine artery blood flow resistance and lower endometrial blood flow in unexplained RPL instances and adequate uterine and endometrial blood flow is a critical precondition for successful implantation and continuation of pregnancy and this explanation was also mentioned by Taher et al., [22].

In the current study, it was found that at a cut off 2.3 or more of uterine artery PI, it can significantly predict the unexplained RPL with 72.73% sensitivity, 94.55%

specificity, 93.0% PPV and 77.6% NPV (table 7) and (figure 9).

Also, it was found that at a cut off 0.85 or more of uterine artery RI, it can significantly predict the unexplained RPL with 80.0% sensitivity, 70.91% specificity, 73.3% PPV and 78.0% NPV. Accordingly, there was statistically significant difference between the Sensitivity, Specificity, PPV and NPV of uterine artery PI and uterine artery RI in prediction of unexplained RPL with P value < 0.001 and therefore, the pulsatility index (PI) is better in the prediction of unexplained RPL (table 4).

Ghazi Rifat [23] concluded that uterine artery Doppler is a good predictor for miscarriage in early pregnancy. Therefore, it should be made a standard screening test to identify women who are at risk of miscarriage so that effective preventative management techniques such as rest, aspirin and heparin, progesterone supplements and other measures can be used.

In our study, Pearson correlation showed that there was no statistically significant linear correlation between uterine arteries' PI and RI and patient's age, BMI and progesterone level P-value >0.05 (table 5).

Ertuğrul et al., [24] also found insignificant correlation between midluteal serum progesterone level and uterine artery PI and RI values ($p > 0.05$).

6. Conclusions:

Serum progesterone had no role in prediction of unexplained RPL. Uterine artery PI and RI had a role in prediction of unexplained RPL, but the PI is better than RI .

Recommendations

Because of these results, it may be possible to recommend the use of transvaginal uterine artery Doppler in women at risk for spontaneous abortion during the midluteal phase of the menstrual cycle .

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