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Moustafa H. Gad Allah
Professor of Obstetrics & Gynecology, Faculty of Medicine – Al-Azhar University, moustafakamello1983@gmail.com

Farid I. Hassan
Professor of Obstetrics & Gynecology, Faculty of Medicine – Al-Azhar University

Mofeed F. Mohamed
Professor of Obstetrics & Gynecology, Faculty of Medicine – Al-Azhar University

Mohamed I. Al-Mohandes
Consultant of Obstetrics and Gynecology, El Galaa Maternity Teaching hospital

Nagham A. El-Amer
Consultant of Clinical Pathology, El Galaa Maternity Teaching hospital

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ORIGINAL ARTICLE

Uterine Artery Doppler and Subendometrial Blood Flow and Serum Progesterone Level in Patients with Unexplained Recurrent Miscarriage

Moustafa Hussein Gadallah [b,*], Farid Ibrahim Hassan [a], Mofeed Fawzi Mohamed [a], Mohamed Ibrahim Al-Mohandes [b], Nagham Abed El-Amer [c]

[a] Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo Egypt
[b] Department of Obstetrics and Gynecology, El-Galaa Maternity Teaching Hospital, Cairo, Egypt
[c] Department of Clinical Pathology, El-Galaa Maternity Teaching Hospital, Cairo, Egypt

Abstract

Background: **Unexplained miscarriage that occurs repeatedly is still a difficult issue for couples and professionals. It affects 2–5% of females attempting to conceive and represents a considerable challenge for physicians.**

Aim: **This study compares women who have unexplained recurrent miscarriages (RMs) with healthy, fertile women to assess uterine artery blood flow, subendometrial blood flow, and serum progesterone levels in these women.**

Patients and methods: **The research was carried out at Al-Galaa Maternity Teaching Hospital; the patients were divided into two groups. The case group: 50 individuals disclosed a history of recurrent, unexplained miscarriages, and the control group: 50 individuals who had at least one term birth and no history of miscarriage.**

Results: **The pulsatility index of the uterine artery especially the mean value, and flow index (FI), vascular index, and vascular FI of the endometrial and subendometrial area, in addition to the serum progesterone level are crucial factors in case of unexplained RM. They affect unexplained RM incidence significantly. The pulsatility index of the uterine artery has an influence on unexplained RM with 74% accuracy. The FI has 95% accuracy, and the vascular FI has 86% accuracy in case of unexplained RM. The serum progesterone level has a 70% accuracy effect on unexplained RM.**

Conclusion: **The study documented that the uterine artery Doppler, endometrial and subendometrial blood flow level, and serum progesterone level affect the incidence of unexplained RM with accuracy ranging between 70 and 95%.**

Keywords: Progesterone, Subendometrial blood flow, Unexplained recurrent miscarriage, Uterine artery doppler

1. Introduction

Three or more spontaneous miscarriages, whether consecutive or not, constitute a recurrent miscarriage (RM). Around 2–5% of couples have RMs. RMs may be caused by a variety of factors, including genetic, anatomical, endocrinological, immunological, microbiological, and environmental factors. However, there are still many miscarriages whose causes are still unknown.[1]

RM is an uncertain etiology that may include several factors, and its diagnosis and management are debatable. Chromosome abnormalities, anatomical conditions, endocrine factors, thrombophilic factors, autoimmune anomalies, and reproductive tract infections are some of the known etiologic reasons. However, unexplained recurrent miscarriage (uRM), which is referred to as RM and seems to be primarily linked to alloimmune variables, affects around 50% of people with the condition.[2]

Endometrial thickness, blood supply, and other variables may influence endometrial receptivity.[3] Recently, increasing focus has been placed on vaginal color Doppler ultrasonography, a noninvasive and simple imaging technique with excellent clinical applications in the identification of endometrial receptivity.[4]

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* Corresponding author at:
E-mail address: moustafakamello1983@gmail.com (M.H. Gadallah).

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When women have RMs owing to decreased uterine perfusion, low-dosage aspirin increases the blood flow velocity through uterine arteries. Blood flow was improved by nitric oxide donors, which may have therapeutic benefits.[5]

As uRM is related to high uterine artery blood flow resistance and poor endometrial blood flow, the existence of healthy uterine and endometrial blood flow is crucial for successful implantation and maintenance of pregnancy.[6] Women who have repeated initial trimetric unexplained miscarriages have altered subendometrial blood flow.[7]

Successful embryo implantation and the avoidance of miscarriage have both been linked to progesterone. In fact, progesterone was among the first pharmaceuticals to be administered in 1950 for the treatment of RMs. One of the first female sex hormones to be identified was progesterone. It is known as 'the hormone of pregnancy' because of its function in the successful implantation of an embryo.[8]

The aim of the study was to compare women who have uRMs with healthy, fertile women to assess uterine artery blood flow, subendometrial blood flow, and serum progesterone levels in these women.

2. Patients and methods

This case–control study was conducted at El-Galaa Maternity Teaching Hospital, and it included 100 patients from January 2018 to June 2021. Women are split into two groups: those who had repeated, unexplained miscarriages (research group, number = 50), and those who have not (control group, number = 50).

The clinical research study is conducted in accordance with the current IRB-approved clinical protocol, relevant policies, requirements and regulations of Al-Azhar University.

2.1. Inclusion criteria

For the research group: women with three or more unexplained miscarriages, having regular menstrual cycles, and not using hormonal or intrauterine devices. Hysterosalpingogram reveals patent fallopian tubes, and no congenital anomalies, adhesions, or masses. The thyroid gland profile is within the normal range. Anticardiolipin antibodies and lupus anticoagulant antibodies of less than 20 Milliliter/liter (MPL) and Gram/liter (GPL).

For the control group: women being not pregnant, having regular cycles, not using hormonal contraception or intrauterine device, and having no history of miscarriage with at least one child born at term.

2.2. Exclusion criteria

For both groups: uterine alteration within the hysterosalpingogram or ultrasonography. Any systemic disease that affects the hemodynamic indices. History of oophorectomy or tubal ligation. After patients' counseling and procedure explanation, a written and informed consent will be obtained to participate in the study.

Each patient was exposed to history taking: personal, medical, surgical, obstetric, and gynecological history with stress on menstrual history, history of pelvic radiation and pelvic chemotherapy or pelvic pathology that can affect the ovarian function.

General, medical, surgical, and gynecological examination with stress on factors that can affect the ovarian function such as obesity, diabetes mellitus, tuberculosis, and thyroid gland disorders. Examinations are performed in the second half of the menstrual cycle. Examinations are performed by using a scanner (GE Voluson 730 Pro 4D, vaginal probe 5–9 MHz). The uterine artery is first assessed using pulsed color Doppler technology. The index of pulsatility is computed. The region of interest is identified using a longitudinal segment of the uterus and a power Doppler placed across the endometrium and the subendometrial region. The endometrial volume is determined using a virtual organized computer-assisted analysis (VOCAL). The vascularization index, which characterizes the vessel density, the flow index (FI), which assesses both vascularity and perfusion, and the vascular flow index (VFI) are all generated using the histogram function. By positioning the caliper myometrial endometrial boundaries, the endometrial thickness is measured. The serum progesterone level is obtained on day 21 of the cycle.

2.3. Data management and analysis

Statistical Package for the Social Sciences (2017; IBM Corp.) was utilized to update, code, tabulate, and introduce the acquired data to a computer (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY). Data were given, and the kind of data gathered for each parameter was appropriately analyzed. To assess the normal distribution of continuous data, Shapiro–Wilk's test was used. For parametric numerical data, mean ± SD, and range were used. Proportion and frequency of non-numerical information and the statistical significance of the variation between the means of the two research groups were evaluated utilizing Student's *t*-test. To investigate the connection between two qualitative variables, the χ^2-test was performed. A valuable tool for assessing the sensitivity and specificity of quantitative diagnostic tests that divide patients into two categories is the receiver operating characteristic curve. Analysis of correlation (using the Spearman/Pearson formula): to determine how strongly two quantitative variables are associated. The degree and direction of the linear link between two variables is defined by the correlation coefficient, which is represented symbolically by the letter '*r*'. Results with a *P* value less than 0.05 or below were deemed substantial.

3. Results

The median right uterine artery PI among the patients' group was 2.56 ± 0.6 (Table 1). The median left uterine artery Pulsatility Index (PI) was 2.59 ± 0.58. The median uterine artery PI was 2.6 ± 0.59 (Table 2).

The mean FI among the cases group was 17.02 ± 4.32. The mean VFI was 0.28 ± 0.13. The median endometrial thickness was 9.89 ± 2.04. The mean endometrial volume was 2.3 ± 0.72 (Table 3).

The median right uterine artery PI among the control group was 2.03 ± 0.51. The median left uterine artery PI was 2.11 ± 0.43. The median uterine artery PI was 2.1 ± 0.44 (Table 4).

The mean FI among the control group was 9.95 ± 1.45. The mean VFI was 0.12 ± 0.08. The median endometrial thickness was 9.74 ± 2.13. The median endometrial volume was 2.21 ± 0.66 (Table 5).

Table 1. Description of right, left, and mean uterine artery PI among patients.

	Mean ± SD	Minimum	Maximum
Right uterine artery PI	2.56 ± 0.60	1.50	3.50
Left uterine artery PI	2.59 ± 0.58	1.80	3.50
Mean uterine artery PI	2.60 ± 0.59	1.60	3.50

Table 2. Description of FI, VFI, endometrial thickness, and endometrial volume among patients.

	Mean ± SD	Minimum	Maximum
FI	17.02 ± 4.32	10.00	25.00
VFI	0.28 ± 0.13	0.10	0.50
Endometrial thickness (mm)	9.89 ± 2.04	6.00	12.50
Endometrial volume (ml)	2.30 ± 0.72	1.30	3.50

FI, flow index; VFI, vascular flow index.

Table 3. Description of right, left, and mean uterine artery PI among controls.

	Mean ± SD	Minimum	Maximum
Right uterine artery PI	2.03 ± 0.51	1.30	2.90
Left uterine artery PI	2.11 ± 0.43	1.60	2.90
Mean uterine artery PI	2.10 ± 0.44	1.60	2.91

Table 4. Description of FI, VFI, endometrial thickness, and endometrial volume among controls.

	Mean ± SD	Minimum	Maximum
FI	9.95 ± 1.45	8.00	12.50
VFI	0.12 ± 0.08	0.01	0.25
Endometrial thickness (mm)	9.74 ± 2.13	6.00	13.50
Endometrial volume (ml)	2.21 ± 0.66	1.15	3.30

FI, flow index; VFI, vascular flow index.

Regarding age, BMI, and parity, there was no substantial variation between the patients and the controls. The difference between cases and controls, however, was very substantial as the patients had lower serum progesterone levels than controls (Table 6).

There was a highly substantial variation between patients and controls regarding right, left, mean uterine artery PI, FI, and VFI with higher levels among patients. However, there was no substantial variation between patients and controls regarding endometrial thickness and endometrial volume.

4. Discussion

This study was conducted to evaluate uterine artery blood flow and subendometrial blood flow and serum progesterone level in women with uRMs compared with normal fertile women.

In the present study, regarding age, there was no statistically substantial variation between the control group and the patient group. The average age of the females in the RPL group was 28.00 ± 6.55 years, which was comparable to the study's average age by Garhy et al.[9] who revealed that contrary to other research, there was no statistically substantial variation between the control group and the sick group.

Surprisingly, results obtained in the Uysal et al.[10] study was that the mean age was higher in the control group compared with the uRMs group, 28.25 ± 3.71 and 26.69 ± 4.4, respectively. However, this was not statistically substantial ($P = 0.176$). In addition, in the El-Mazny et al.[11] study, the mean ± SD age of the unexplained infertility group was 29.41 ± 3.15 (28.40–30.42) and the median± SD age of the control group was 30.12 ± 3.44 (29.02–31.22) However, this was not statistically substantial (P = 0.0.339).

Regarding serum progesterone (ng/ml), a very statistically substantial variation between the control group and the patient group was discovered in the present investigation. In accordance with these

Table 5. Comparison between patients and controls as regards personal and medical (sociodemographic data) characteristics.

	Groups		*P*	Significance
	Control	Cases		
	Mean ± SD	Mean ± SD		
Age (years)	28.88 ± 6.76	28.00 ± 6.55	0.510[a]	NS
Serum progesterone (ng/ml)	15.20 ± 1.65	14.04 ± 1.41	0.001[a]	HS
BMI	26.22 ± 1.26	25.95 ± 2.56	0.514[a]	NS
Parity (%)				
P_1	14 ± 28.0	22 ± 44.0	0.088[b]	NS
P_2	14 ± 28.0	16 ± 32.0		
$P > 3$	22 ± 44.0	12 ± 24.0		

HS, highly significant.
[a] Student's *t*-test.
[b] χ^2-test.

Table 6. Comparison between patients and controls as regards right, left, mean uterine artery PI, FI, VFI, endometrial thickness, and endometrial volume.

	Group		*P*	Significance
	Control	Cases		
	Mean ± SD	Mean ± SD		
Right uterine artery PI	2.03 ± 0.51	2.56 ± 0.60	0.001[a]	HS
Left uterine artery PI	2.11 ± 0.43	2.59 ± 0.58	0.001[a]	HS
Mean uterine artery PI	2.10 ± 0.44	2.60 ± 0.59	0.001[a]	HS
FI	9.95 ± 1.45	17.02 ± 4.32	0.001[a]	HS
VFI	0.12 ± 0.08	0.28 ± 0.13	0.001[a]	HS
Endometrial thickness (mm)	9.74 ± 2.13	9.89 ± 2.04	0.731[a]	NS
Endometrial volume (ml)	2.21 ± 0.66	2.30 ± 0.72	0.487[a]	NS

FI, flow index; HS, highly significance; VFI, vascular flow index.
[a]Student's *t*-test.

findings, a research by Ziegler et al.[12] hypothesized that low progesterone values would enhance uterine vascular impedance.

By contrast, the El-Mazny et al.[11] study showed that neither the control group (18.50 ± 5.25) nor the unexplained infertility group (20.03 ± 5.53) had significantly different progesterone levels ($P = 0.209$).

In agreement with this study results regarding right uterine artery PI, left uterine artery PI, and median uterine artery PI, the Garhy et al.[9] study revealed that uterine artery PI was considerably greater (2.6 ± 0.36) in the group with RMs than in the control group (1.7 ± 0.27) ($P = 0.000$). In the research group, there was a substantial positive connection ($r = 0.8$, $P = 0.00$) between UAPI and recurrent abortion.

The Funda et al.[13] study results showed that the research subgroups' left and right uterine arterial PI values were statistically substantially greater than those in the control group (primary RPL; right PI: 2.81 ± 0.69, left PI: 2.72 ± 0.61, $P < 0.001$; secondary RPL; right PI: 2.63 ± 0.59, left PI: 2.6 ± 0.57, $P < 0.001$).

Correspondingly, in a study performed by Wahab et al.[6] when the luteal phase uterine artery PI of 40 patients with uRMs was examined, it was discovered that it was substantially greater compared with the control group of women who had at least one term pregnancy and no history of loss. RMs and uterine artery PI were shown to have a positive connection. When compared with the control group, the uterine artery PI in the miscarriages group was considerably greater ($P < 0.01–0.0001$).[5]

Nakatsuka et al.[14] evaluated uterine perfusion and vascular variations among patients with RPL, and they compared 32 habitual miscarriage patients with 62 fertile patients according to their uterine artery PI values. In the habitual miscarriage group, they found substantially greater uterine artery PI values compared with the control group. Uterine artery PI was substantially greater in women who had recurrent pregnancy loss (2.70 ± 0.47) compared with the control women (2.09 ± 0.39) ($P > 0.001$).

Conceding with this study results regarding flow index (FI), Garhy et al.[9], study found significantly higher sub endometrial indices in the control group compared to recurrent miscarriage group, a significant negative correlation was found between FI (r = -0.79, P = 0.00) and recurrent miscarriage in the study group. Similarly, Taher et al.[7], the FI was higher in the control group (23.975±4.1716) than in the case group (19.138 ± 6.9013), which was statistically significant (P = 0.002).

In addition, Tan et al.[1] revealed the midluteal phase endometrial volume and endometrial vascular characteristics of individuals with RMs or healthy pregnancies. The results between the two groups showed that there was a significant difference regarding FI (27.04 ± 11.97) (31.34 ± 17.84) ($P = 0.003$), respectively.

According to the Abdel-Razik et al.[5] research, there was a substantially reduced subendometrial vascularization index, FI, and VFI in the miscarriage group compared with the control group ($P < 0.01–0.0001$) when uterine artery and subendometrial blood flow indices were compared between the control and miscarriage groups. When compared with the control group (16.89 ± 3.5), FI was considerably lower in the study group (10.30 ± 1.05).[6]

In the El-Mazny et al.[11] study group, the endometrial FI was considerably ($P = 0.031$) decreased in the unexplained infertility group (25.24 ± 8.57) compared with the control group (29.55 ± 8.98).

In this research, there was significant statistically substantial variation found between the control group and the patient group regarding VFI. This result was matched with a study by Tan *et al.*[1], which showed that VFI values were substantially lower in the RPL patients (0.60 ± 0.39) compared with the control group (2.17 ± 1.89).

The Taher et al.[7] study results showed a statistically substantial ($P = 0.048$) difference between the VFI in the control group (1.2048 ± 1.11649) and the RM group (0.71254 ± 0.6522). Similarly, in the Abdel-Razik et al.[5] study there was a substantially reduced subendometrial VFI in the miscarriage group (0.17 ± 0.03) as compared with the control group (0.21 ± 0.01) ($P < 0.01–0.0001$).

In agreement with the present study results as regards the endometrial thickness (mm) and endometrial volume (ml), the Garhy et al.[9] study showed that between the two groups, there was no substantial change in endometrial volume or thickness. Moreover, this result agreed with the Tan et al.[1] study.

The Funda et al.[13] study showed that endometrial thickness was found to be significantly lower in both primary and secondary miscarriages than that in the control group (11.2 ± 2.5, 9.7 ± 2.9, and 9.5 ± 3.1, respectively). Therefore, with these findings, they consider that uterine perfusion defects are not only an independent factor in RPL etiology, but they also cause RMs by negatively affecting endometrial maturation.

In a different research, endometrial thickness varied between the study group (RM group) and the control group, although there was no statistically substantial variation between the two (9.7 ± 1.8 mm vs. 9.7 ± 1.4 mm, $P = 0.9$). In addition, there was no variation between the two groups in terms of endometrial volume ($P = 0.6$).[6] In the El-Mazny et al.[11] investigation, there were no substantial differences in endometrial thickness ($P = 0.435$) or volume ($P = 0.210$) between the unexplained infertility group and the control group.

In the Nakatsuka et al.[14] study, endometrial thickness and PI in the uterine artery were substantially different between the control group and the group that had recurrent pregnancy loss (11.0 ± 2.5) and (9.8 ± 2.9), respectively, which was statistically substantial ($P < 0.04$).

Endometrial thickness and blood progesterone levels were shown to be correlated. Progesterone levels in both groups rose along with endometrial thickness.[15]

4.1. Conclusion

The study documented that the uterine artery Doppler, endometrial and subendometrial blood flow level, and serum progesterone level affect the incidence of uRMs with accuracy ranging between 70 and 95%.

Conflicts of interest

There is no conflict of interest.

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