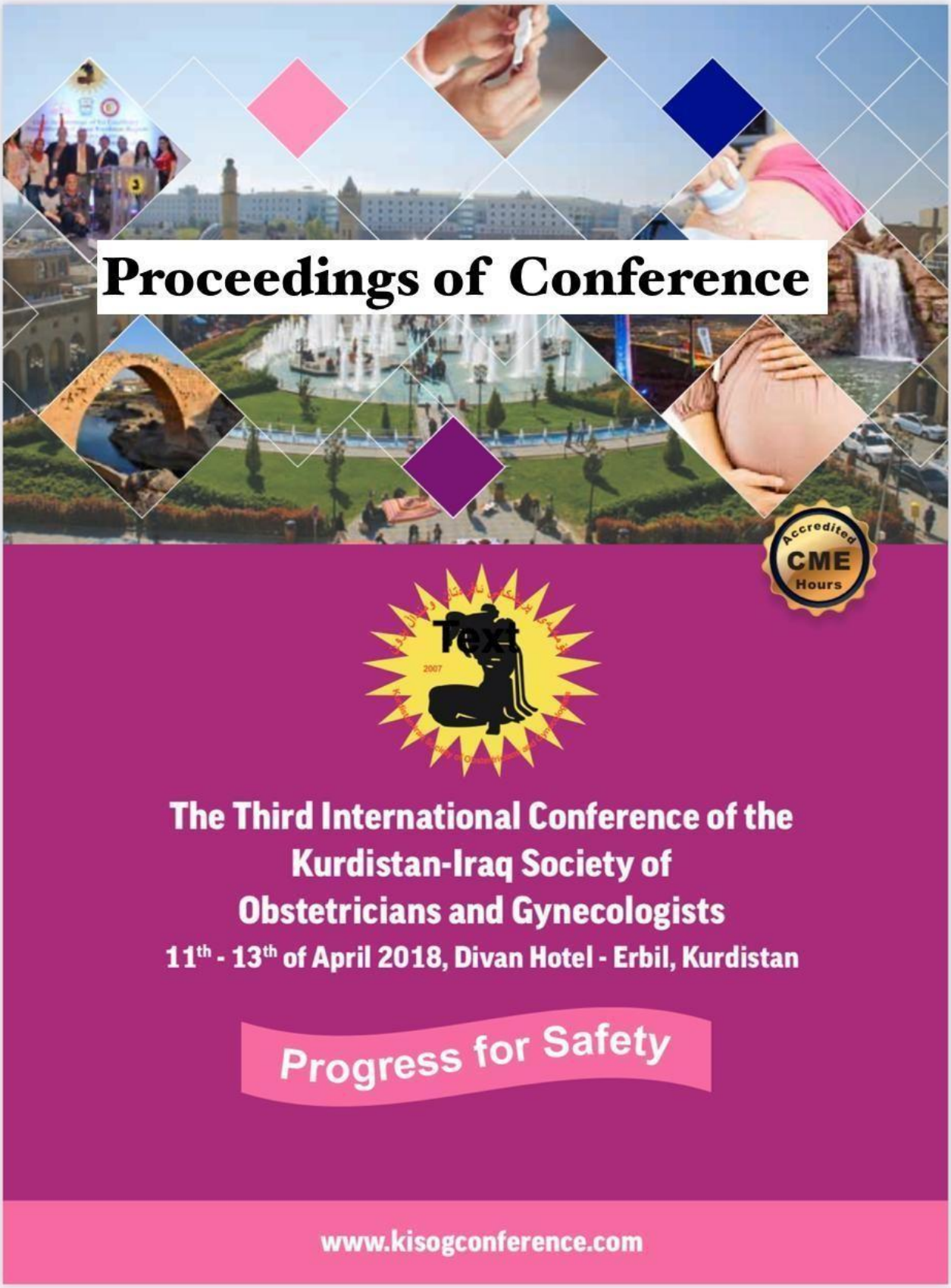
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A comparison between uterine artery blood flow in fertile and unexplained infertile women by Doppler ultrasound using pulsatility index and resistance index

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ABSTRACT

Background and objectives:

Infertility is inability to conceive after one year of regular unprotected intercourse. Unexplained infertility is present if the basic fertility investigations are normal. The objective of this study is to investigate the use of uterine artery blood flow as a cause of unexplained infertility (using pulsatility index, resistance index) and compare them to fertile women.

Methods:

A prospective cohort study was performed on 70 patients (35 fertile and 35 with unexplained infertility patients) in Sulaymaniyah Maternity Teaching Hospital, Kurdistan Region, Iraq, during October 2016 to December 2017. Transvaginal color Doppler ultrasound was done in the mid luteal phase (day 21 - 24) for uterine artery by using pulsatility index and resistance index.

Results:

The age of the patients ranged from 20 - 39 years. The uterine artery pulsatility index was significantly higher in the unexplained infertile women (mean ± SD = 2.78 ± 0.615) than fertile women (mean ± SD = 2.42 ± 0.325). The uterine artery blood flow resistance index was

significantly higher in unexplained infertile group (mean ± SD = 0.899 ± 0.066) than fertile women (mean ± SD = 0.83 ± 0.054).

Conclusions:

Unexplained infertility is associating with decreased uterine artery blood flow and increase uterine artery resistance (pulsatility index and resistance index) when compared with fertile women.

Keywords: Unexplained Infertility; Pulsatility Index; Resistance Index; Fertility; Transvaginal color Doppler study

Introduction:

Infertility is defined as inability to conceive after one year of regular unprotected intercourse and it is present in about 15% of the couples who are trying to conceive[1, 2]. There are two types of infertility: primary infertility ─ in which the woman has never conceived ─, and secondary infertility ─ the women has history of previous pregnancy[3]. Moreover, the rate of spontaneous pregnancy is 57%, 72%, 85%, 93% after three months, six months, one year, and beyond two years respectively[4]. There is a 50% chance of conceiving for couples after the first year and most of them start investigations for infertility after one year[4]. However, when there is a suspected reason(s) for infertility and if the female is 35 years or above, the investigation should be started sooner[4]. Furthermore, the most frequent causes of infertility are: ovulation disorder (27%), tubal factor (22%), male factor (25%), unexplained (17%), and others (9%)[5].

Unexplained infertility is present when there is no identifiable cause and this term can be applied to 15-30% of couples depending on the number of investigations performed and the degree of evaluation[6]. The following are basic investigations of infertility:

1- Determination of ovulation which is by the followings:

a. Menstrual pattern: a regular cycle of 25-35 days, duration of 3-7 days of bleeding, mid cycle pelvic pain and sometimes slight bleeding, and primary dysmenorrhea are most likely signs of ovulation[5].

b. Serum progesterone: it can be measured in the mid luteal phase to detect ovulation. In addition, mid luteal phase is approximately seven days from the next expected period e.g. day 21 in a 28 days cycle. Moreover, progesterone level during follicular phase is <2 ng/ml and it is >4-6 ng/ml in luteal phase during ovulation[5].

2- Tubal patency and it can be detected by the followings:

a. X-ray hysterosalpingography by installing water-based or oil soluble radio opaque contrast through a cannula attached to the cervix [3].

b. Laparoscopy and dyehydrotubation which is the gold standard investigation of tubal assessment.

c. Hysterosalpingocontrast sonography in which a small balloon catheter is inserted into the uterine cavity through the cervix and a vaginal scan is performed during injection of 2-5 ml galactose granule medium through the catheter. Furthermore, when there is flow the length of tube is patent[3].

3- Male factor: seminal fluid analysis (SFA) is a mainstay for the assessment of male factor. Moreover, SFA should be performed after three days of abstinence but no longer than one week and the sample should reach laboratory within one hour after ejaculation while holding it at body temperature. Furthermore, one normal result is enough to exclude male factor, but if abnormalities were found the test should be repeated after the first sample, although resolution of transient insults which lead to defect in sperm production may not be obvious until three months after the insult[3].

Another investigation for infertility is Doppler ultrasonography. Doppler phenomenon was first described by Christian Doppler in nineteenth century[7]. Furthermore, the pitch of sound of a moving object changes when the space between the source of the sound and the observer changes, which is called Doppler shift and it is a consequence of Doppler phenomenon[7]. Accordingly, when the frequency of emitted sound from the stationary source is stable, and its insonation angle is known, the Doppler shift can be measured because it is correlated to the velocity of the relative movement between the transducer and the source[7]. Moreover, blood contains numerous cells at different velocities; thence, Doppler signal is a combination of different Doppler shift frequencies[8].

When the angle between the ultrasound beam and the longitudinal axis of the vessel is known, the frequency shift can be changed to velocity[9]. In addition, the measurement of this angle is important during the calculation of the velocity[9]. Moreover, the Doppler measurement is considered reliable when the insonation angle is $<60^0$ because when the frequency shift decreases to zero, the insonation angle reaches 90^0 [9]. Therefore, velocity measurement is commonly used in pulsed studies[9].

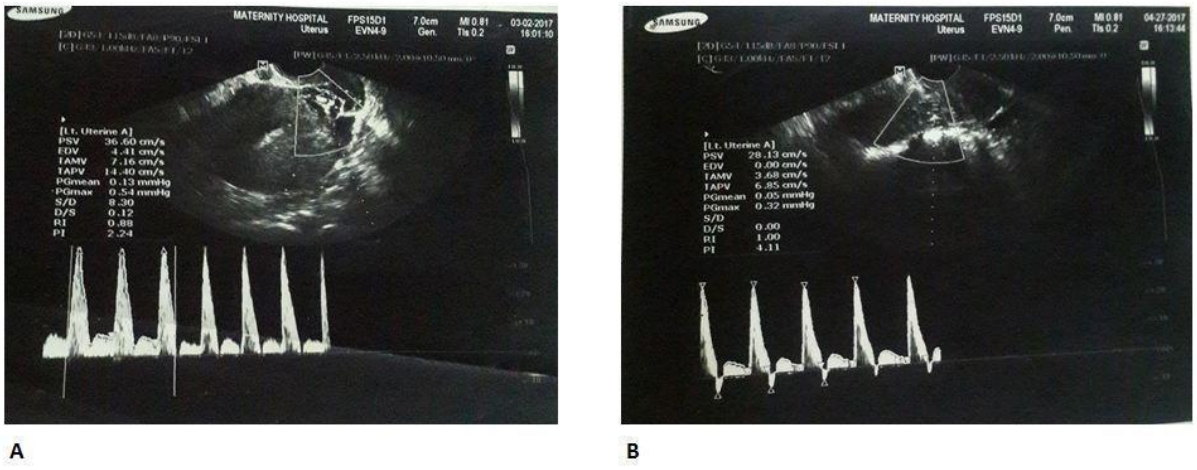
Uterine artery provides most of the blood supply of uterus and assessment of its vascular properties are expected to provide information about the ability of uterus to allow implantation of the fertilized ovum and pregnancy progression[10]. For such assessment, Doppler ultrasound is the investigation of choice, and it is noninvasive and easy to use equipment[10]. Moreover, uterine artery blood flow can be expressed by pulsatility index (PI) and resistance index (RI)[11].

In a normal cycle, there is a higher early and late uterine artery PI with lower levels during the mid-cycle or luteal phase[12-13]. In addition, some studies showed that there is low resistance to flow during late follicular and mid luteal phases which are the time when endometrium thickens and its vascularity increases[13-15]. The decreased PI during luteal phase with the increase of blood velocity and its vascularity indicates that there is increased uterine perfusion, and preparation for implantation and increased rate of pregnancy[16-18]. Moreover, uterine artery blood flow is a useful method of assessment of uterine receptivity in assisted reproduction program[19].
In this study, our aim was to find out whether the uterine artery blood flow is a cause of unexplained infertility (using PI and RI) by comparing them to fertile women in our population.

Patients and methods:

We performed a prospective cohort study on 70 patients who were admitted in Sulaymaniyah Maternity Teaching Hospital, Sulaymaniyah City, Kurdistan Region, Iraq. Research Ethics Committee of Kurdistan Board of Medical Specialties approved the study proposal and a formal acceptance letter was obtained from Sulaymaniyah Maternity Teaching Hospital before starting the study.
The patients that participated in the study were referred from private clinics and from the gynecology unit of Sulaymaniyah Maternity Teaching Hospital. Additionally, Verbal consent was taken from all participants. Furthermore, the study was conducted during October 2016 to December 2017 on 70 patients; 35 fertile women and 35 patients with unexplained infertility.
The inclusion criteria were as follows:
1- Regular menstrual cycle.
2- Unprotected regular intercourse.
3- Normal ovulatory function, normal SFA and patent fallopian tubes which was assessed by hysterosalpingography and laparoscopy.
The exclusion criteria were as follows:
1- Patient taking hormonal treatment or ovarian stimulation during the cycle.
2- Past history of any chronic medical disease.
3- Smoking.
4- Tubal factor, ovulatory factor and male factor and pelvic pathologies like uterine fibroid.

Transvaginal color Doppler ultrasound (CONOACER7, model 2014) was performed in the mid-luteal phase of the cycle for the participants in the radiology department of the same hospital by the same operator who was experienced in Doppler ultrasound to avoid inter-observer variability. Moreover, after taking consents from the all patients and in lithotomy position, transvaginal color Doppler ultrasound was performed during morning hours (from 9:00 am - 12:00 pm) to avoid circadian changes of the blood flow. Furthermore, both the PI and RI were measured for both the right and left uterine artery followed by measuring the mean of each of PI and RI for both uterine arteries (Figure 1).



A B

Figure (1) shows the transvaginal color Doppler ultrasound results (pulsatility and resistance indices) for a fertile woman (A) and an unexplained infertile woman (B)

We used "IBM SPSS Statistics version 20" computer software program for the analysis of the data. Additionally, we considered a P-value of ≤0.05 as statistically significant and a P-value of <0.001 as very highly significant.

Results

The mean ± SD (Standard Deviation) ages of all the 70 patients were (29.3 ± 5.1) years and ranged from 20 to 39 years.

A statistically significant decreased uterine artery blood flow and increased uterine artery resistance were found in women with unexplained infertility by using measurements of PI and RI (Table 1).

Table (1) shows association of fertility with the pulsatility and resistance indices of uterine arteries assessed by transvaginal Doppler ultrasonography

Comparison of PI and RI between groups		Mean ± SD	P-value
PI	Group A (Fertile group)	2.42 ± 0.325	<0.001
	Group B (Unexplained infertile group)	2.78 ± 0.615	
RI	Group A (Fertile group)	0.83 ± 0.054	<0.001
	Group B (Unexplained infertile group)	0.899 ± 0.066	

The advance in age was significantly associated with increased PI and RI and subsequently with unexplained infertility (Table 2).

Table (2) shows association of age (year) with both the pulsatility and resistance indices according to both groups of fertile and unexplained fertility participants

Comparison of age with PI and RI in the groups		Mean ± SD	P-value
Group A (fertile)	Age (year)	29.66 ± 4.54	<0.001
	PI	2.42 ± 0.325	
Group B (unexplained infertility)	Age (year)	29.03 ± 5.77	<0.001
	PI	2.78 ± 0.615	
Group A (fertile)	Age (year)	29.66 ± 4.54	<0.001
	RI	0.83 ± 0.054	
Group B (unexplained infertility)	Age (year)	29.03 ± 5.77	<0.001
	RI	0.899 ± 0.066	

Pulsatility index was significantly higher in patients with secondary infertility (Table 3).

Table (3) shows association of the types of infertility with pulsatility index

Types of infertility	PI (Mean±SD)	P-value
Primary (60%)	2.7 ± 0.54	<0.001
Secondary (40%)	2.9 ± 0.72	

Resistance index was also significantly higher in patients with secondary infertility (Table 4).

Table (4) shows association of the types of infertility with resistance index

Types of infertility	RI (Mean±SD)	P-value
Primary (60%)	0.89 ± 0.064	<0.001
Secondary (40%)	0.91 ± 0.071	

Discussion

Transvaginal color Doppler ultrasonography is a noninvasive test for the evaluation of uterine artery impedance, blood flow changes, and anatomical details of the uterus[20-22]. Moreover, uterine receptivity is regulated by numbers of factors such as uterine perfusion, which is important for the achievement of normal pregnancy[23]. During luteal phase of normal menstrual cycle, the impedance to uterine artery reduces to the lowest values to increase endometrial perfusion and help implantation[12, 21, 24-28]. Therefore, a high resistance during luteal phase can be a cause of unexplained infertility[24].

The cause of increased uterine artery impedance in infertile women may be explained by attenuation in the uterine artery response to the circulating ovarian hormones[12]. In addition, optimum uterine receptivity occurs when the mean PI of both uterine arteries is between two and three, while implantation and pregnancy rate significantly decreases when mean PI is above three to four[29-30]. Furthermore, the theory of impaired uterine artery ─ increased impedance to blood flow ─ as a cause for unexplained subfertility was first mentioned by Goswamy et al. by using transabdominal pulsed wave Doppler[26].

The study of Zenneni et al.[31] which was conducted on 50 fertile and 50 unexplained infertile women found that the mean RI was 0.79 and 0.78 for unexplained infertile and fertile women respectively with statistically insignificant association (P-value = 0.9), and the mean PI was 1.93 and 1.78 for unexplained infertile and fertile women respectively with statistically insignificant association (P-value = 0.29). Moreover, the study of Rozik et al.[32] in Egypt showed a mean ± SD PI of (1.09 + 0.22) and (1.64 + 0.52) for fertile and unexplained infertile women respectively with statistically significant association (P-value of <0.001), and a mean ± SD RI of (0.60 + 0.07) and (0.68 + 0.11) for fertile and unexplained infertile women respectively with no significant changes (P-value = 0.72), although the RI was higher in unexplained infertile group.

In the current study, there was significantly higher PI in the mid-luteal phase of unexplained infertile women compared to fertile women (P-value of <0.001), and there was also significantly higher RI in the mid-luteal phase of unexplained infertile women in comparison to fertile women (p-value of <0.001) as shown in Table (1). In comparison, the study of Yakota et al.[24] who studied 63 infertile women during periovulatory period in Japan at 2000, showed a significantly lower PI during conception than non-conceptive cycles. In addition, the study of El-Mazny et al.[33] showed a

significantly (P-value = 0.003) higher PI for unexplained infertile women (mean ± SD = 2.12 ± 0.49) than fertile women (mean ± SD = 1.81 ± 0.42), and significantly (P-value = 0.007) higher RI for unexplained infertile women (mean ± SD = 0.89 ± 0.23) than fertile women (mean ± SD = 0.76 ± 0.19). Furthermore, we also found some other studies who found an increased PI and RI in unexplained infertile women with a significant associations[23, 27, 34].

Conclusions

Our findings support that unexplained infertility is associated with a decrease in uterine artery blood flow and an increase in the uterine artery resistance (PI and RI) when compared with fertile women. We recommend performing more researches on how to eliminate the age factor as a confounder and how to treat this increased uterine artery impedance.

Conflict of interest

The authors report no conflicts of interest

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