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The Role of Uterine and Subendometrial Arteries Doppler in Patients with Early Missed Abortion to Predict the Need for Surgical Evacuation, Prospective Observational Study

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Abstract: Background: The need for dilation and curettage was greatly decreased by the pharmacological treatment of early pregnancy loss. Prognostic markers of good outcome, though, have not been established. **Objectives:** The present research was intended to study the efficacy of uterine artery and subendometrial vasculature Doppler studies to predict whether or not we need D & C if conservative management failed in patients with missed first trimester abortion. **Materials and Methods:** This prospective observational study was conducted on 250 women with early pregnancy loss in the first trimester attended to the emergency department of the hospital from March 2018 to March 2020. These patients were enrolled in order to evaluate the efficacy of uterine artery and subendometrial vasculature Doppler studies to predict whether or not we need D & C if conservative management failed in patients with missed first trimester abortion. **Results:** There was a significant difference in the means of PI, RI and subendometrial vasculature between the 2 groups. In addition, the cut-off value for PI was 2.96 at 93% sensitivity and 54.3% specificity for predicting the need of D & C or spontaneous abortion. **Conclusions:** Uterine artery Doppler evaluation can predict the need for D & C due to incomplete miscarriage, after management of missed abortion using misoprostol.

1. Introduction

The possibility of conceiving represents about 40% during the menstrual cycle period and about 33% of the conceptions may not result in delivery of good baby. Miscarriages are the failure of progressing in pregnancy and sometimes occur without explained causes. Women who experience miscarriage for two times or more must seek help from professionals [1].

Also, miscarriage was also recognized as the loss of pregnancy before the second trimester of gestation and the majority of miscarriage conditions (80%) occur during the first trimester [2].

Management and evaluation of women during the first trimester are safe options for avoiding pregnancy loss [3]. Also, misoprostol and uterine dilatation and curettage (D & C) can be connected with higher success rates in about all the cases of pregnancy loss during the early period of gestation [4].

Using uterine sonography for assessing the miscarriages cases could evaluate the volume of the remaining ovular tissue in the uterine cavity and decidual thickness. However, sonography fails to exactly predict the consequence of the treatment and the conservative management [3].

Recently, assessing the contents of the uterine cavity was done using color Doppler also; it could be used for exploring the persistent association between maternal circulation and the residual of trophoblasts [5].

Assessing the retained material volume, the availability of blood flow and other Doppler changes would provide a successful prediction of conservative treatment thus lessen the requirements for D & C.

Aim of the Work

The purpose of this research is to assess the efficacy of uterine artery and subendometrial vasculature Doppler studies to predict whether or not we need D & C if conservative management failed in patients with missed first trimester abortion.

2. Patients and Methods

I.   Study design:

After approval of the scientific committee of Obstetrics and Gynecology department of Al-Azhar University Hospital and consent of patients included in the study, this prospective observational study was conducted on 250 women with early pregnancy loss in the first trimester attended to the emergency department of the hospital from March 2018 to March 2020. These patients were enrolled in order to evaluate the efficacy of uterine artery and subendometrial vasculature Doppler studies to predict whether or not we need D & C if conservative management failed in patients with missed first trimester abortion.

Setting:

Al-Azhar University Hospital of Damietta.

❖   **Inclusion criteria: -**

A)   Primary inclusion criteria:-

1- All women should be in the first trimester (1st-13 weeks).

2- Pregnancy with ultrasound evidence of losing the activity of the fetal heart.

3- Length Crown-Rump equal to or greater than 7 mm with no cardiac activity, or less than 7 mm with no cardiac activity, but with no growth after one week.

4- Presence of an empty sac with a mean diameter of the sac equal to or greater than 20 mm without an embryonic pole or a medium diameter of the sac less than 20 mm without any change in size on rescan after one week.

❖   **All patients were subjected to:**

♦   **Clinical Evaluation:**

A.   Clinical history taking: -

B.   Ultrasound examination: -

Transvaginal scan was done for confirmation of pregnancy loss based on the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists (Green-top guideline No. 25. London: RCOG; 2006.) including:

-      Empty sac with no detectable embryo in the sac and a mean sac diameter equal to or greater than 20 mm.

-      Empty sac with no detectable embryo in the sac and a mean sac diameter less than 20 mm with no change in size on rescan after one week.

-      A large embryonic pole with crown-rump length equal to or greater than 6 mm with no cardiac activity.

-      Crown-rump length less than 6 mm, no cardiac activity but with no growth after one week.

❖   **Exclusion criteria: -**

A) Primary exclusion criteria:-

1- Ectopic pregnancy, complete or incomplete abortion.

2- Uncontrolled blood pressure, mitral stenosis, severe asthma or glaucoma, known allergies to prostaglandins or prostaglandin contraindications.

3- Multiple gestation, with visible cardiac activity of one or more of than.

4- Heavy vaginal bleeding or hemodynamic instability.

5- Miscellaneous including current anticoagulant therapy, hemoglobin <10 g/dL, body temperature > 38°C.

Management and follow up

Primary intervention:

The patients were treated with 1600 μg divided into two doses of vaginal misoprostol, given 4 hours apart. A uterine ultrasound examination was conducted eight hours after beginning the procedure.

Primary outcome:-According to response to the given misoprostol the patients were either:-

• Patients with complete failure of misoprostol medications with persistent gestational sac after misoprostol administration (**Group IA**). These patients were submitted to D & C and excluded from the study (secondary exclusion).

• Patients with no complete failure of misoprostol medication **(Group IIA)**:-

-No complete failure with presence of remnants, but with severe bleeding and / or hemodynamically unstable. These patients were submitted to immediate D & C and excluded from the study (secondary exclusion).

- No complete failure in any endometrial thickness with heterogeneous features in the uterine cavity without gestational sac and endometrial midline echo distortion, hemodynamically stable. These patients were submitted to secondary intervention.

• Patients with complete success of misoprostol medication with complete abortion were also secondary excluded **(Group IIIA)**.

B)   Secondary exclusion criteria:-

1- Including patients with complete failure of misoprostol medications i.e. persistent gestational sac in spite of misoprostol administration in full dose (**Group IA**).

2- Including patients with no complete failure of misoprostol medications **(**presence of heterogeneous features in the uterine cavity with no gestational sac and endometrial midline echodistortion at any endometrial thickness.**),** with severe bleeding and / or haemodynamically unstable.

3- Including patients with complete success of misoprostol medication i.e. (complete abortion) **(Group IIIA)**.

C)   Secondary inclusion criteria:-

Patients with no complete failure of misoprostol medications (Group IIA), hemodynamically stable after full dose of misoprostol administration i.e. (at any endometrial thickness, the existence of heterogeneous features in the uterine cavity without

gestational sac and endometrial midline echo distortion.)

Secondary intervention:

Group IIA patients (candidates of secondary intervention) were discharged on the following advice:-

1- To attend after two weeks, if everything is stable.

2- To contact the investigator, if they developed:-

A) Any change of body temperature or development of malodourous vaginal discharge (markers for infections).

B) Development of excessive bleeding, greater than the customary menstrual blood loss or passage of blood clots.

Group IIA patients were appointed to two week visit to reassess their state of miscarriage and to reevaluate the effect of misoprostol by symptoms profile, pelvic ultrasound and Doppler studies of the uterine artery and subendometrial vasculature.

Methodology of Doppler study:-

- Uterine artery and sub endometrial vasculature Doppler studies.

Uterine artery Doppler study include uterine artery pulsatility (PI) and resistance (RI) indicines, while the sub-endometrial vasculature study evaluated presence or absence of flow in sub-endometrial vasculature).

A sampling gate set at 2 mm was utilized with a pulsed wave Doppler to cover the entire vessel, ensuring that the insonation angle was lower than 30°. & sub-endometrial vasculature flow were performed by one operator who had experience more than 5 years in this field to avoid variability in the results using a Voluson ultrasound multi-frequency trans-vaginal and abdominal device with a trans-vaginal transducer of 5 MHz.

Secondary outcome:-according to ultrasound scan and Doppler study the patients were either:-

- Patients with complete abortion with endometrial thickness equal to or less than 15mm (**Group IB**) they were be tertiary excluded.

- Patients with incomplete abortion with endometrial thickness more than 15mm (**Group IIB**):-

• Patients with incomplete abortion with endometrial thickness more than15mm with considerable vaginal bleeding and /or haemodynamically unstable or developed infections were also tertiary excluded and managed with D & C.

• Patients with incomplete abortion with endometrial thickness more than 15mm and haemodynamically stable they were submitted to tertiary intervention.

- Patients did not attend and loss of their follow up (**Group IIIB)**, those patients were also tertiary excluded.

C) Tertiary exclusion criteria:-

1- Including patients with complete abortion with endometrial thickness less than 15mm at two weeks follow up (**Group IB**).

2- Including patients with incomplete abortion with endometrial thickness more than 15mm, but with considerable bleeding and /or haemodynamically unstable or developed infections at two weeks follow up.

3- Loss of follow up patients (**Group IIIB**).

C) Tertiary inclusion criteria:-

Including patients with incomplete abortion with endometrial thickness more than15mm at two weeks follow up visit (**Group IIB), hemodynamically stable**.

Tertiary intervention:-

Group IIB Six weeks later (eight weeks after initial diagnosis), patients were appointed to revisit the hospital), and transvaginal ultrasound scan was performed.

Tertiary outcome: According to ultrasound scan of six weeks follow up visit the patients were either:-

- Patients with complete abortion with endometrial thickness equal to or less than 15mm (**Group IC**).

- Patients with incomplete abortion with endometrial thickness more than 15mm (**Group IIC**), these patients were submitted to final intervention.

- Patients did not attend and loss of their follow up (**Group IIIC**), those patients were finally excluded.

Final intervention

Including patients with **Group IIC** and they were managed with D & C.

Final outcome: All patients recruited in the study were allocated into one of the following groups:-

- **(Group ID)** All cases of late complete abortion including (Group IB & Group IC).

- **(Group IID)** All cases submitted to late D & C including (Group IIB with considerable vaginal bleeding & infections & Group IIC**).**

Consequently, patients were divided into two groups:

1. All cases of late complete abortion after Doppler study and misoprostol administration **(Group ID)**.

2. All cases submitted to late D & C after Doppler study and misoprostol administration **(Group IID).**

*Group ID and Group IID** were statistically studied correlated to Doppler findings to evaluate predictive value of Doppler indices in prediction for need of E & C or not.

Statistical analysis

Using the Windows Statistical Package of Social Science (SPSS) software (Standard version 24), the

data was analyzed. Data normality was first tested with the Kolmogorov-Smirnov test of a single sample. Numbers and percentages were used to describe qualitative data. Continuous variables were provided for parametric data as mean ± SD (standard deviation) and for non-parametric data as a median (min-max). The Mann Whitney test (non-parametric data) compared the two groups. Sensitivity and specificity at different cut off points were tested by ROC curve. The significance threshold is set at the 5 % level (p-value) for all the above statistical tests performed. When (p ≤0.05), the findings were considered significant. The lower the p-value obtained, the results are more significant.

3. Results

Table 1: Demographic data among the studied group

Demographic data	Study group (n=250)
Age/ years **Mean ± SD** 20-24 y 25-34 y 35-46 y	**28.31±5.08** 71 (28.4%) 135 (54%) 44 (17.6%)
Residence **Urban** **Rural**	179 (71.6%) 71 (28.4%)
Educational level **Less than secondary education** **Secondary and university educated**	157 (62.8%) 93 (37.2%)
Occupation **Housewife** **Workers**	182 (72.8%) 68 (27.2%)
BMI **<30** **≥30**	107 (42.8%) 143 (57.2%)
Smoking **Yes** **No**	18 (7.2%) 232 (92.8%)

Table 2: Obstetric history among the studied group

Obstetric history	Study group (n=250)
Parity **P ≤3** **P > 3**	188 (75.2%) 62 (24.8%)
Previous spontaneous first trimester miscarriage **Yes** **No**	30 (12%) 220(8%)

The parity was less than or equal 3 among most of the subjects (75.2%) and 24.8% among the rest. Only 12% of the patients experienced previous spontaneous first trimester miscarriage and the rest have not experienced miscarriage.

Table 3: Uterine artery Doppler among the studied group

Uterine artery Doppler	Study group (n=250)
Pulsatility index *Median (Min-Max)*	3.61 (1.23-7.89)
Resistance index *Median (Min-Max)*	0.87 (0.58-1.00)
Subendometrial vasculature	

The mean Pulsatility index (PI) was 3.61 and the resistance index (RI) was 0.87.

Table 4: Comparison of GI D and GII D regarding uterine artery Doppler

Uterine artery Doppler	GI D (n=48)	GII D (n=17)	Test of significance	P value
Plusatility index *Median (Min-Max)*	3.55 (2.19-8.01	2.57 (1.16-3.97)	Z=3.29	0.002*
Resistance index *Median (Min-Max)*	1.00 (0.66-1.00)	0.81 (0.58-0.98)	Z=2.23	0.026*
Subendometrial vasculature **Absent** **Present**	41 (85.4%) 7 (14.6%)	4 (23.5%) 13 (76.5%)	χ^2=22.57	≤0.001*

GID=GIB+GIC=30+18; GIID =GII B+GII C =8+9=17

Z: Mann Whitney test, χ^2: Chi square test, *significant p <0.05

The Pulsatility index and resistance index were substantially higher in group I with complete abortion than group II with incomplete abortion. The subendomertrial vasculature index was significantly present among group II than group I.

Table 5: Receiver operating characteristic curve (ROC) for prediction of GID by PI and RI

	AUC	95% CI		Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
		Lower	Upper						
PI	0.793	0.685	0.901	>2.96	93.5%	54.3%	64.4	90.5	74.7%
RI	0.676	0.567	0.885	>0.91	90.9%	54.3%	65.2	86.4	70.1%

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

The Doppler Pulsatility index sensitivity and specificity were 93.5% and 54.3% respectively with 64.4 PPV and 90.5% NPV with high accuracy reaching 74.7%. The Doppler resistance index sensitivity and specificity were 90.9% and 54.3% respectively with 65.2% PPV and 86.4% NPV with high accuracy about 70.1%.

4. Discussion

Bleeding and abortion are the most popular reasons of early pregnancy seeking medical advice, and spontaneous abortion is a clinically recognized loss of pregnancy prior to viability [6]. Consequently, if a screening test is available that can indicate the probability of abortion in the near future, effective management techniques and prophylactic strategies can be provided to save a life. [7].

There is ample evidence for the advantage of uterine artery Doppler ultrasound to evaluate uteroplacental perfusion and predict future pre-eclampsia development, fetal growth restriction, placental abruption, and second trimester stillbirth [7], Even so, researchers have not reached a concrete consensus so far on the use of uterine Doppler measurements to predict adverse effects between 6-14 weeks in the early stages of pregnancy and determine whether or not patients need D & C. Therefore, the present study sought to determine any correlation between measurements of the Doppler uterine artery and to determine the sensitivity and specificity of the indices of uterine artery pulsatility (PI) and resistance (RI), with a view to detecting patients with early pregnancy loss that require D & C. These measurements may be used to predict or classify women who have difficult pregnancies or require D & C [8], also, the need for uterine evacuation in cases of early pregnancy loss (delayed abortions or incomplete miscarriages, missed abortion) has also been a matter of controversy in recent decades. Since surgical procedures have possible risks and may lead to complications including infection, hemorrhage and perforation of the uterus, the decision to use medications or to adopt an attitude of expectation is deemed reasonable, secure and effective. The success rate calculated in a reasonable time frame, such as 2 weeks [3], prevented D & C from being used.

The previously mentioned studies reviewed the efficiency of uterine Doppler artery in prediction of early abortion but little studies have found an association between the Doppler artery and the prediction and management of abortion complications. In the present study Doppler artery was used to predict the proper management of abortion by missorbitol or with D & C in which we found that the Doppler results helped us to differentiate between women who would achieve full resolution (group I) and those who should

stay under supervision in group II which needs D & C, in the same respect to our study, Casikar et al., 2012 used color Doppler to evaluate the contents of the uterine cavity to explore continuous communication among the residual trophoblasts and maternal circulation [5]. Also, Subjective qualitative power Doppler colour scoring (PDCS) can forecast the probability of successful expectant management of incomplete abortion as a result of widespread equipment availability, In pregnant women, several research have analyzed the patterns of uterine artery blood flow, focusing on PI and RI. Both indices have end-arteriolar impedance quantitative data [9] and consequently on local vascular resistance and velocity of blood flow.

Other studies showed the same results when using Doppler power to verify the existence of RPC after abortion or birth. *In women who had spontaneous first-trimester miscarriages, Alcazar and Ortiz [10] used color Doppler to diagnose RPC.* They examined asymptomatic and clinically stable women with first-trimester spontaneous abortion. In Doppler ultrasonography, eighteen women suspected of obtaining retained products of conception (RPC) undergone curettage. Of those, sixteen women have been reported to have RPC on histopathology. There is no clear clinical importance of scanning, diagnosing RPC and curetting clinically symptomless women. They concluded that ultrasonography with transvaginal color Doppler is beneficial for detecting or excluding the existence of retained trophoblastic tissue after spontaneous miscarriage in the first trimester and selecting patients for expectant management. However, they did not use Doppler results to forecast effective expectant management of incomplete abortion, unlike in our research [10].

Van den Bosch et al. [11] have also shown that the color Doppler test is clinically beneficial in confirming or excluding residual trophoblastic tissues. They found retained tissue in women who were clinically symptomatic in most cases. In other words, power Doppler was used to validate what they may have clinically suspected. While they then handled their women expectantly with RPC, they again did not associate color Doppler results with the probability of good expectant management [11].

Above that, in order to minimize the incidence of unnecessarily invasive procedures, **Ben-Ami et al.** showed that the combination of both clinical and ultrasonographic assessment is recommended prior to curettage. Thus reiterating the need for physical and ultrasonographic assessments in order to prevent needless curettage, they did not use a Doppler power to evaluate the RPC qualitatively; nor did they associate these results with expectant management, that is the foundation of our research. [12].

Also, recent studies have shown the possible utility of Doppler uterine artery assessment to forecast the need for uterine curettage in patients receiving medical care for early pregnancy loss [13].

In other studies, the success rates of using Doppler studies were from 71% to 84% for expectant attitudes [3], and, full abortion was found in 83 to 86 % of patients for follow-up periods of 1 week to 4 weeks in cases where misoprostol was administered [14].

In the present study, the Doppler Pulsatility index sensitivity and specificity were 93.5% and 54.3% respectively with 64.4 PPV and 90.5% NPV with high accuracy reaching 74.7%. The Doppler resistance index sensitivity and specificity were 90.9% and 54.3% respectively with 65.2% PPV and 86.4% NPV with high accuracy about 70.1%.

Respectfully, the absence of blood flow in the residual intrauterine trophoblastic tissue has been shown to be correlated with a substantially higher success rate of expectant management when compared to the presence of flow [5]. This novel approach can be beneficial in quantifying the chances of successful expectant management on the primary scan in those women with an incomplete miscarriage that is compatible with our research.

In other words, it showed that only the mean PI value was significantly linked to the pregnancy outcome [8]. This result is consistent with the result that the unilateral elevation of uterine arteries PI in the first trimester was correlated with the subsequent incidence of abortion [15], **Romero-Gutiérrez et al.** however noticed that increased RI was the parameter correlated with the adverse outcome of pregnancy [16]. In addition, the findings of this study showed that the cut-off value of 2.96 for the PI was highly sensitive and specific to the miscarriage prediction. In addition, uterine artery PI was more than 2.5 in the aborted patients, while the uterine artery PI value was 2.5 or less in those who achieved the term. [15], on the other hand, due to the limited number of patients who were pregnant and reached term in their sample, the researchers could not predict the outcome of pregnancy based on this cut-off value. This would be the case for the other research which also failed to involve the cut-off for the indexes as it was a cross-sectional research performed between high-risk pregnancies and lacks a control group and follow-up to assess the pregnancy outcome of the registered women [17].

To our very best knowledge, there is a lack of studies that has focusing on early pregnancy with an average gestational age of 9 weeks to identify the best index and its cut-off value for use as a screening test for early pregnancy failure and prediction of the outcomes and necessity of D & C.

This study has some limitations including the limited sample size of each group and the failure to resolve the confounders were considered to be the constraints of this research. For uneventful early pregnancy, the absolute values of the uterine artery PI and RI were not verified, reflecting a study limitation. Although the mean PI reference ranges for the uterine artery are well defined, covering gestation from 6 to 41 weeks, more studies are needed to determine the identical normality curves in women who have spontaneous miscarriage and are treated expectantly. This reference range would be useful in verifying the use of uterine artery Doppler to treat early-pregnancy loss cases.

There was a substantial difference in mean PI, RI and subendometrial vasculature between the 2 groups. Moreover, at 93 % sensitivity and 54.3 % specificity, the cut-off value for PI was 2.96 to predict the need of D & C or spontaneous abortion.

Conclusion & Recommendations:

The present study provided evidence that Doppler assessment of the uterine artery can forecast the need for D & C in cases of incomplete abortion following missed abortion management with misoprostol. Accordingly, we may recommend introducing this Doppler studies as a routine screening test for identifying patients with early missed abortion who may need D & C.

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