

To operate or to wait? Doppler indices as predictors for medical termination for first trimester missed abortion

Wassan Nori¹, Muna Abdulghani², Ali B Roomi^{3,4,*}, Wisam Akram⁵

¹ Department of Obstetrics and Gynecology, College of Medicine, Al-Mustansiriyah University, 10052 Iraq

² Department of Radiology, College of Medicine, Al-Mustansiriyah University, 10052 Iraq

³ Ministry of Education, Directorate of Education Thi-Qar, Thi-Qar, 64001 Iraq

⁴ College of Health and Medical Technology, Al-Ayen University, Thi-Qar, 64001 Iraq

⁵ Consultant Obstetrician and Gynecologist, AL-Yarmook Teaching Hospital, 10015 Iraq

*Correspondence: alibadr205@gmail.com; dr.ali_bader@alayen.edu.iq (Ali B Roomi)

DOI:10.31083/j.ceog.2021.01.2215

This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Submitted: July 08, 2020 Revised: September 11, 2020 Accepted: September 17, 2020 Published: February 15, 2021

Purpose: Missed abortion is a common obstetrical problem with a high incidence. Evidence supports a change in approach from the traditional dilatation and curettage to medical; however, few studies have investigated the prediction success of the medical approach. This study investigates whether first trimester missed abortion can be successfully terminated using Doppler indices, such as resistance index (RI) and pulsatility index (PI), as predictors. **Material and Method:** In this prospective study, the sample is made up of 78 patients, with a first trimester missed abortion range of 6-13 weeks of pregnancy who meets the maternal parameters as well as transvaginal Doppler indices, RI and PI. The participants were subdivided into 3 groups based on their response to sublingual misoprostol and weeks needed to terminate as Groups I (43/78), II (26/78), and III (9/78) aborted in the first, second, and third weeks, respectively. **Results:** Age, BMI, and gestational age of dead fetus were not significant for Groups I, II, and III with $P=0.13$, $P=0.13$, and $P=0.35$, respectively. Parity and delivery mode showed significant differences ($P < 0.0001$) between group means of PI and RI. PI for Group I plus II and Group III are 1.53 (0.75-2.70) and 1.58 (1.10-2.10), respectively. RI for Group I plus II and Group III are 0.71 (0.50-1.00) and 0.80 (0.69-0.92), respectively. The coefficient of correlation proves that RI is the primary predictor of successful termination of a first trimester missed abortion with a cut-off value of 0.74 with associated sensitivity and specificity of 68.7% and 56.7%, respectively. **Conclusions:** Increased parity and a history of vaginal delivery, in addition to measured RI, were predictors of successful termination of a first trimester missed abortion. These results may be used in counseling patients to decide safest and most suitable option to terminate a first trimester missed abortion, depending on their demographic criteria and ultrasound scores.

Keywords

Missed abortion; First trimester; Misoprostol; Doppler; Resistance index; Pulsatility index

1. Introduction

Missed abortion is a common obstetrical condition with a 20% incidence of all clinically diagnosed pregnancies. It has received considerable attention in the past two decades

as there is an increased focus on medical rather than surgical options. This is due to the introduction of new drugs, such as misoprostol and mifepristone, which have emerged as effective options for medical termination. Medical termination carries the advantage of outpatient treatment, lifting much of the burden on maternity hospitals [1, 2]. Misoprostol, a synthetic prostaglandin agonist originally used to treat peptic ulcer, was accidentally discovered to be an abortifacient agent. Compared with a surgical method, it has been the focus of many studies, regarding its dosing and route of administration, either alone or in combination with other drugs, with varying success rates and safety profiles [3, 4]. Treatment failure is a well-acknowledged subject by most obstetric practitioners and has been investigated by many researchers; some relate it to maternal parameters and others to the drug chosen. Ultimately, those with failed treatment will need dilatation and curettage [5]. Predicting the causes of treatment failure has gained much interest. The first report (in the form of a case report in non-conclusive concepts) on the successful use of Doppler to predict the medical option was produced in the past few decades. In 2009, an evaluation of the effectiveness of uterine arteries in predicting pregnancy outcome was reported in the Journal of Reproduction of Domestic Animals, after which many studies on human reproduction emerged, relating pregnancy outcome and the fate of on-going pregnancy [6].

Fortunately, uterine artery Doppler is easily evaluated in obstetrics and gynecology (OBG) clinics; the changes in the normal pattern of uterine artery indices, PI and RI, during the first trimester were recorded. Doppler study stands out as a non-invasive investigation with high acceptance rates and minimal side effects [7]. Little is known about the role of Doppler in predicting the success of medically terminated first-trimester abortion, predicting the causes remains a challenge. We hypothesized that a doppler study, measuring both resistance index (RI) and pulsatility index (PI), of uterine ar-

teries, performed before undergoing treatment might predict the success of medically terminated first-trimester missed abortions and the time required to complete it. The importance and originality of this study are that it explores the relationship between Doppler indices in patients with a first trimester missed abortion and the success of medical termination, along with carefully selected maternal parameters that are valuable to clinicians.

2. Materials and methods

2.1 Study design

This is a prospective cohort observational study that evaluates Doppler indices, PI and RI, in patients with a first trimester missed abortion, as a predictor of the termination success by misoprostol.

2.2 Sample and sampling technique

Participants who met the selection criteria and were willing to participate in the study were identified through their first trimester missed abortion diagnosis, ranging from 6-13 weeks, which was determined based on their last menstrual cycle, or the criteria for diagnosis endorsed by the Royal College of Obstetricians and Gynecologists.

2.3 Study site and setting

This study was conducted in the OBG department of Al-Yarmouk Teaching Hospital, Baghdad/Iraq; a tertiary treatment center that receives thousands of patients every month. This hospital has a variety of specialties, such as general surgery, cardiology, orthodontics, pediatrics, neuropsychology, maternity, and family medicine.

2.4 Data collection procedure

The Department of Obstetrics and Gynecology at Al-Yarmuk Teaching Hospital ethics committee provided ethical approval for the study and verbal consent was sought from all participants. The data were collected from March 2019 to March 2020. A total of 100 patients were recruited; however, 22 patients were excluded based on the exclusion criteria; 78 patients participated in the study. Complete blood count, blood group and rhesus factor, fasting and random blood sugar, blood urea, serum fibrinogen, coagulation profile, and thyroid hormone (T3, T4, and TSH) tests were conducted on all participants. To understand the prediction criteria of our sample, we recorded maternal parameters, such as age, parity, mode of delivery (vaginal or caesarian), and mean gestational age of the dead fetus. Doppler study was performed on all participants before they embarked on the study regimen. We confirmed the diagnosis and excluded other gynecological problems, such as molar pregnancy and uterine fibroid, and others listed in the exclusion criteria. Doppler examination studies were performed by the same radiologist to decrease inter-observational differences. The examination was conducted by placing the patient in a supine position, using vaginal probe 8-4 MHZ, logic P5 TOSHIBA machine. A sagittal plane to the uterus that shows the cervix and its internal os was implemented. The vaginal transducer was gently

introduced and tilted from side to side. We identified uterine arteries at the internal os level with the aid of a color flow mapping. Subsequently, pulsed wave Doppler at a sampling gate gaged at 2 mm covered the entire vessel. We ensured an angle of insonation $< 30^\circ$. The mean PI and RI of the left (L) and right (R) arteries were calculated when 3 similar consecutive waveforms were obtained, and the mean of the R and L artery measurements was calculated. The values of the PI and RI were measured and recorded for R and L uterine arteries, and the mean of every participant was determined, provided the difference was $< 5\%$.

2.5 Inclusion criteria

Pregnant women in their first trimester, in gestational age of 6-13 weeks, diagnosed with missed abortion and admitted to the outpatient department for voluntary termination. These were invited to participate in this study after its aim and workflow were explained. A detailed history was recorded, and examinations were performed.

2.6 Exclusion criteria

1. Multiple pregnancies, molar pregnancy, and ectopic pregnancy.
2. Patients with maternal chronic diseases, such as diabetes, hypertension, and chronic arterial disease.
3. Known contraindication to misoprostol, for example, asthma.
4. Congenital uterine abnormality, uterine fibroid or polyp, adenomyosis, and endometriosis.
5. Patients with anemia or known blood dyscrasias or on anticoagulant drugs.
6. Patients who tested positive for TORCH screen and anticardiolipin and antiphospholipid antibodies.
7. Patients who were diagnosed with congenital malformation of the fetus, whether dead or alive.

All participants were assigned medical treatment that was administered on an outpatient basis: 600 μg misoprostol tablets were administered sublingually in a dose of 2-3 tablets every 4 hr (a total of 6 tabs per day) along with a mild analgesic for a 3-day course. In the follow-up phase of the study, participants were asked to return to the hospital if they experienced severe bleeding to assess whether complete abortion had occurred or further surgical intervention was needed.

Complete abortion was defined by a history of the passage of clots and tissues, a vaginal examination revealing a closed os; a confirmation pelvic ultrasound (not Doppler) was used as proof that complete abortion had taken place. Those patients were given antibiotics and analgesics and sent home.

After a 1-week treatment period, some patients committed abortion (good responders); others fail to abort (poor responders) and were offered a second and third course depending on their response. The patients were stratified into 3 groups based on their response to treatment; Group I (43/78) were the good responders who aborted within the first week and Groups II (26/78) and III (9/78) were the poor responders who aborted within the second, and third weeks, respec-

tively. By the end of the third week, for those who failed to respond to medication, elective termination by curettage was done under general anesthesia Fig. 1.

3. Statistical analysis

Statistical analysis of data was performed using SAS (Statistical Analysis System-version 9.1). The test of normality, using the Shapiro-Wilk test, showed that the data were not normally distributed; therefore, the means were compared, using the Mann-Whitney test. Chi-square test or Fisher test (as applicable) was used for the descriptive measures. $P < 0.05$ was considered statistically significant. The criterion between RI and PI was assessed by using the partial least square curve (PLS) and the coefficient marker of matrix mathematics. Thus, the eigenvalue was used for multiple independent parameters, such as PI and RI and the dependent parameter, the gestational age of the dead fetus. Positive eigenvalues above 1 indicate a correlation between the two studied parameters, especially the higher positive values. On the other hand, eigenvalues below 1 or in the negative range indicate that there is no correlation between the two measured parameters.

A receiver operating characteristic curve was used to identify the validity of the marker (RI) as an indicator of pregnancy loss. The marker cut-off value was generated according to the area under the curve. The analysis was performed using MedCalc Software. The sensitivity (a probability that the test will be positive when the infection is present).

The specificity (a probability that the test will be negative when the infection is absent).

MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2016) SAS.2010.SAS/STAT Users Guide for Personal Computer. Release 9.13.SAS Institute, Inc., Cary, N.C., USA.

Finally, Poisson regression was used to measure the risk ratio of surgical intervention.

4. Results

A total of 78 patients with a confirmed first-trimester abortion participated in this study; some of their maternal parameters are presented in Table 1. The age, BMI, and gestational age of dead fetus were not statistically significant with $P = 0.13$, $P = 0.13$, and $P = 0.35$, respectively; however, parity and delivery mode were significant with $P < 0.0001$ and $P < 0.0001$, respectively, which were also significant for all participants and the individual groups. The differences in the means of PI and RI are highlighted in Table 2; it can be seen that PI for Group I plus II and Group III are 1.53 (0.75-2.70) and 1.58 (1.10-2.10), respectively. On the contrary, RI for Group I plus II and Group III are 0.71 (0.50-1.00) and 0.80 (0.69-0.92), respectively. Closer inspection of the table shows that RI has a better predictive value than PI with $P = 0.02$ and $P = 0.62$, respectively.

The PLS curve in Fig. 2 shows the correlation between Doppler indices, PI and RI, as independent variables and the

gestational age of the dead fetus as a dependent variable in the successful termination of abortion. Surprisingly, RI was the only parameter to reach a statistically significant correlation with the gestational age of the dead fetus with an eigenvalue of 2.77, contrary to that of PI (-0.8), ascribe as a successful predictor.

Receiver operating curve (ROC) analysis was used to calculate the cut-off value for RI; the result was 0.74, any reading below this number is more likely to have a successful medical induction of abortion, as shown in Fig. 3.

As shown earlier, not all the patients aborted within the first week; some failed and continued to the second and third weeks; hence those who aborted in the first week were considered the reference group. A risk ratio was calculated with the aid of Poisson regression to accurately predict the risk of surgical intervention specific to each group; as shown in Table 3, the risk ratios were estimated to be 1.3 and 4.7 for the second and third weeks, respectively.

5. Discussion

Unique adaptations in placental morphology and function have increasingly been acknowledged and well described with Doppler-derived hemodynamic parameters. PI and RI are commonly used to monitor fetal well-being in clinical practice, but whether they significantly influence the type of termination of missed abortion have not been adequately investigated.

Increased parity is among the maternal parameters that best predict good responders. Prior studies by Kim *et al.* portrayed such association, which is contrary to that of Reeves *et al.* and Ehrnstén *et al.*, who stated that the possibility of a successful outcome decreases as gestational age and parity advance since the stretching of uterine muscles and loss of muscle integrity lead to poor response to medical termination. This relationship was most striking in \geq para 5 patients; this may explain the apparent contradiction with the current study as the mean parity was 4 in our patients [8-10]. This study shows there is a strong relationship between predicting good responder and vaginal delivery. This agrees with the results of Kim *et al.*, who declared that vaginal delivery was associated with higher and more rapid success rates. Caesarian delivery tends to alter the success of a good responder because the scarred site will be considered a weak point in disturbing uniform myometrium and its contractility, not to overlook the increased penetration by trophoblasts to the myometrium, making it difficult to expel [8, 11]. Maternal age and gestational age of the dead fetus are not statistically significant; the same finding was reported in a study by Kim *et al.* In contrast, earlier findings by Ehrnstén *et al.* suggested that most distinct factor for surgical intervention risk was a 9-week gestational age or more at the time of treatment; the study results do not support this. This inconsistency may be due to the larger sample size. Moreover, the mean age of the participants was (8.4) weeks less than the cut-off value proposed by Ehrnstén L *et al.* [8, 10].

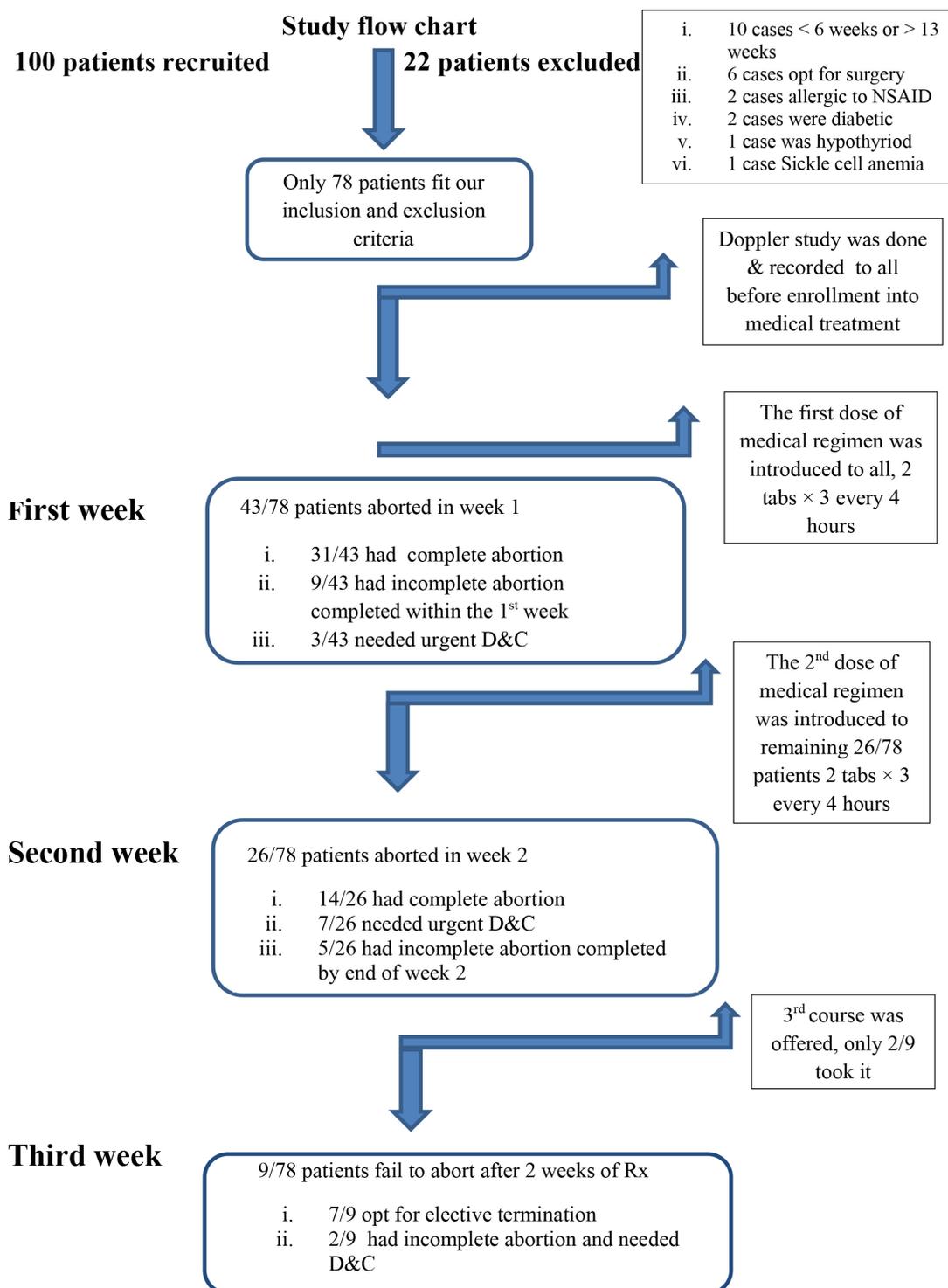


Fig. 1. The study flow chart showing how patients were enrolled and excluded, and the divisions of the study sub-groups.

From the PLS curve and its generated eigenvalue, the RI but not the PI stands out as significantly correlated to the success of medical termination with a cut-off value of 0.74; below which medical treatment will be successful, and above which medical treatment will most likely fail, with increased hazards of surgical intervention. It is promising when this figure is compared with the one expressed by Sonek *et al.* where

both RI and PI correlate with the success rate; this may be explained by the larger sample size used in their study [12]. There are similarities between the results of this study and the results of Guedes-Martins *et al.* that described the use of PI and RI as a predictor of medical management of incomplete abortion. Their results suggested that retained products of conception will affect PI and RI, causing both to increase,

Table 1. The demographic data in all participants under study and for each group individually (I, II, and III) what was significant was highlighted with * which was parity and delivery mode, they were significant in overall and for each group individually.

	All n (%) 78 (100)	Group I 43 (55.2)	Group II 26 (33.3)	Group III 9 (11.5)
Age (Years)	20-24 20 (25.6) <i>P</i> = 0.13	10 (23.3) <i>P</i> = 0.25	8 (30.7) <i>P</i> = 0.29	2 (22.2) <i>P</i> = 0.72
	25-34 34 (43.5)	19 (44.2)	10 (38.6)	5 (55.6)
	35-44 24 (30.7)	14 (32.5)	8 (30.7)	2 (22.2)
Parity	010 (12.8) <i>P</i> < 0.0001*	4 (9.3) <i>P</i> < 0.0001*	4 (15.4) <i>P</i> < 0.001*	2 (22.2) <i>P</i> = 0.18
	≥ 1 68 (87.2)	39 (90.7)	22 (84.6)	7 (77.8)
BMI	≤ 24 32 (41) <i>P</i> = 0.13	13 (30) <i>P</i> = 0.33	15 (57.7) <i>P</i> = 0.006*	4 (44.4) <i>P</i> = 0.88
	25-29 28 (35.9)	16 (37)	9 (34.6)	3 (33.4)
	≥ 30 18 (23.1)	14 (33)	2 (7.7)	2 (22.2)
Delivery Mode	CS26 (33.3) <i>P</i> < 0.0001*	13 (30.2) <i>P</i> < 0.0001*	8 (30.7) <i>P</i> = 0.006*	5 (55.6) <i>P</i> = 0.30
	NV 40 (51.3)	25 (58.1)	13 (50)	2 (22.2)
	NVCS 2 (2.6)	1 (3.3)	1 (3.8)	0 (0)
	Null 10 (12.8)	4 (9.4)	4 (15.5)	2 (22.2)
Meanest Gestational age for dead fetus	8.78 ± 2.48	8.42 ± 2.28	9.11 ± 2.71	9.27 ± 2.70 <i>P</i> = 0.35

Table 2. Comparison of the average (min-max) pulsatility (PI) and resistance (RI) indices in the uterine arteries between groups (I + II) and III, the testing was done once for all participants before embarking into the study, only RI stand out as a reliable predictor with a meaningful *P*-value 0.02.

	Group I+II (n = 69)	Group III (n = 9)	<i>P</i> -value
PI	1.53 (0.75-2.70)	1.58 (1.10-2.10)	0.62
RI	0.71 (0.50-1.00)	0.80 (0.69-0.92)	0.02*

**P* is significant at 0.05.

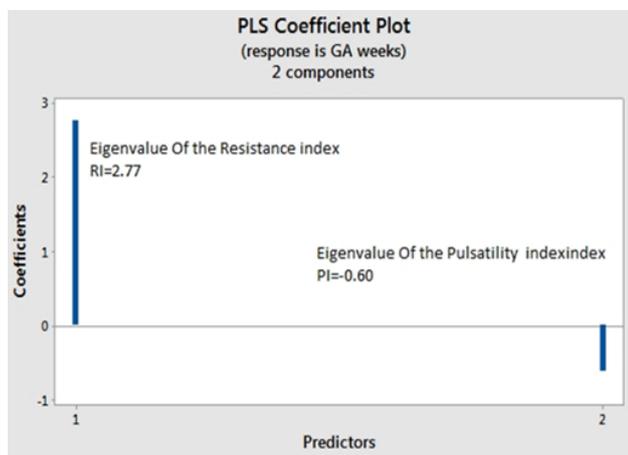


Fig. 2. Partial PLS curve for generating a coefficient of correlation, Eigenvalues; both doppler indices were challenged to detect the most meaningful correlation, it was illustrated as RI to be a significant predictor for successful termination.

necessitating further surgical intervention. The researchers used both mifepristone and misoprostol for treatment; different settings, drugs, and another type of abortion were used. In addition, in line with this conclusion, Hameed *et al.* used color Doppler imaging instead of PI and RI in managing cases of incomplete abortion [13, 14].

The use of PI and RI were the focus of many studies that investigated their effect on predicting pregnancy and deliv-

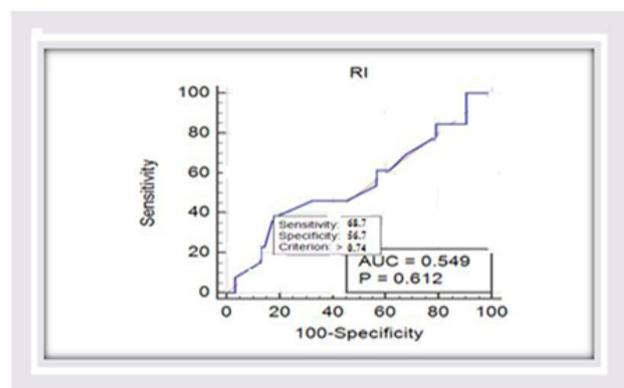


Fig. 3. Receiver operation curve ROC for RI, it was generated to assess the validity of RI as a marker for termination success, a cut off value of RI of 0.74 was concluded with its associated sensitivity and specificity of 68.7, 56.7 respectively.

ery outcomes rather than predicting abortion outcomes as in this study. RI was studied; its reference value was established before and in early pregnancy. Women who were deemed to have missed abortion were classified; for every 0.1 increase in RI, there is an associated 18.7 increase in the risk of abortion [1, 15].

As for those deemed to be experiencing pregnancy-induced hypertension (PIH), intrauterine growth restriction (IUGR) were reported to have higher Doppler indices dur-

Table 3. The risk ratio for failed induction of abortion by Misoprostol was given after being calculated with Poisson regression, we were able to predict the risk of having surgical interference by taking group I [the good responders] as a reference value. The more participants take time to abort the more likely they will need surgery.

Number of D and C	Risk Ratio	95% Confidence Interval
First week	Reference group	
Second week	1.355	0.32-5.59
Third week	4.77	1.13-19.54

ing the pre-pregnancy and early pregnancy states. This was the basis for the therapeutic trial of added aspirin and progesterone drugs that decrease their levels close to the level of the general population [16–18]. Trayanov *et al.* compared RI levels in patients with threatened abortion and normal population reporting no statistical differences. Surprisingly, this was not observed in the study by Khong *et al.* that reported a high and significant RI upon a comparison between normal population and patient deemed to have a first trimester missed abortion and later on PET and IUGR [16, 19]. It should be highlighted that there are discrepancies in RI values that have been reported in different literature. This can be attributed to the differences in study design, sample size, and, most importantly, the criteria for selecting enrolled subjects. A deeper insight reveals that the outcome will be more meaningful if enrolled subjects were selected from the high-risk group rather than the general population. Furthermore, if these subjects were combined with maternal characteristics, the validity will be substantially higher [20]. To explain the study results, a search was made for factors that influence the RI, thereby causing the RI to rise and producing a poor respondent who is resistant to medical termination.

The RI is calculated as the ratio between the mean pressure and the mean volume of blood flow. Consequently, an increase in blood viscosity or an increase in the resistance or a reduction in the radius of blood vessels will be a probable cause [7]. A wide range of causative factors is implicated, keeping in mind the possibility of interference from multiple factors. RI values represent changes in the entire system and are unlikely to be altered by a single factor. Some of these causative factors include oxidative stress, hypoxia, alteration in placental gene expression and endothelial injury, failure of the second wave devascularization of spiral arteries in placental bed, and local release of vasoactive substance [19, 21].

The ROC analysis produced a cut-off point of 0.74 for RI, with associated sensitivity and specificity of 68.7 and 56.7, respectively. The relatively low sensitivity and specificity reached can be explained by the sample distribution. Groups I and II had relatively comparable numbers while group III had a markedly low number. This discrepancy in the distribution led to sampling bias. Moreover, sampling was made from one center; more diverse patients from multiple centers could have added the variance needed to achieve better sensitivity. Another probable factor is the heterogeneity of the causes of a first trimester abortion, and heterogeneity in the modified pattern of vascularity of the myometrium during early preg-

nancy, which affects artery indices. A bigger sample size and a more strict gestational age would have added more credibility to the results and not compromised them. It is advisable to overcome these challenges as they limit the validity of the conclusions reached.

We established the risk of surgical intervention on a poor responder. Those who aborted in the first week (good responders) were considered as the reference group. From that group, based on the weeks, a Risk Ratio was generated to predict the need for surgical intervention. It was clear that the more time elapses, the higher the risk was since it increased from 1.4 to 4.6 in the second and third weeks, respectively. The novelty of this study is that most of the earlier studies addressed the estimated RI in relation to the prosperity and health of on-going pregnancy. So far, very little attention has been paid to the role of Doppler in predicting response for a medical termination among patients with missed abortions. To the best of our knowledge, this is the first study, at least in Iraq, to correlate maternal and Doppler attributes in designing predictive module for patients with missed abortion. This study may serve as a base for further research that will address the implication of the RI in the termination of pregnancies at a higher gestational age.

6. Conclusions

Abortion is commonly practiced. There is a challenge to its management, whether to operate or to wait for a medical termination. Doppler indices were proposed as a means to predict a patient's fitness for the best medical option. The main finding of this study is that the RI measurement may serve as an effective predictor of successful termination, along with increased parity and vaginal delivery. These findings may help patients to make the best and the most appropriate choice, guided by their clinician, based on their demographic characteristics and Doppler indices.

Author contributions

Wassan Nori: wrote the paper, designed the concept, collected the data, scientific editing and revision. Muna Abdulghani: collected the data, performed the experiments and dopplers study, scientific editing and revision. Ali B. Roomi: designed the concept, scientific editing and revision. Wisam Akram: conducted the statistical analyses, scientific editing and revision.

Acknowledgment

The study was supported by the staff of AL-Yarmouk hospital in the collection of samples that are gratefully acknowledged.

Conflict of interest

The authors declare no competing interests.

References

- [1] Henkel A, Shaw KA. Advances in the management of early pregnancy loss. *Current Opinion in Obstetrics and Gynecology*. 2018; 30: 419-424.
- [2] Brady PC, Pocius KD. Spontaneous abortions. *Handbook of consult and inpatient gynecology 2016* (pp. 179-200). Springer. 2016.
- [3] Wu HL, Marwah S, Wang P, Wang QM, Chen XW. Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis. *Scientific Reports*. 2017; 7: 1-9.
- [4] Singh N, Aggarwal R, Shikha D, Goel SK. Comparison of management of missed abortion by the medical and surgical method [intra-vaginal misoprostol vs suction evacuation]. *International Journal of Contemporary Surgery*. 2018; 6: 83-87.
- [5] Sindiani AM, Rawashdeh HM, Alshdaifat EH, Altal OF, Yaseen H, Alhowary AA. The association between repeated doses of vaginal PGE2 (Dinoprostone, Prostin®) and both maternal and neonatal outcomes among women in the north of Jordan. *Clinical and Experimental Obstetrics & Gynecology*. 2020; 47: 329-334.
- [6] Blanco PG, Arias D, Rube A, Barrena JP, Corrada Y, Gobello C. An experimental model to study resistance index and systolic/diastolic ratio of uterine arteries in adverse canine pregnancy outcome. *Reproduction in Domestic Animals*. 2009; 44: 164-166.
- [7] Ferreira AE, Mauad Filho F, Abreu PS, Mauad FM, Araujo Júnior E, Martins WP. Reproducibility of first-and second-trimester uterine artery pulsatility index measured by transvaginal and transabdominal ultrasound. *Ultrasound in Obstetrics and Gynecology*. 2015; 46: 546-552.
- [8] Kim JI, Park IY, Yim JM, Cheon JY, Yun HG, Kwon JY. Serum β -hCG concentration is a predictive factor for successful early medical abortion with vaginal misoprostol within 24 hours. *Obstetrics and Gynecology Science*. 2017; 60: 427-432.
- [9] Reeves MF, Monmaney JA, Creinin MD. Predictors of uterine evacuation following early medical abortion with mifepristone and misoprostol. *Contraception*. 2016; 93: 119-125.
- [10] Ehrnstén L, Altman D, Ljungblad A, Kopp Kallner H. Efficacy of mifepristone and misoprostol for medical treatment of missed miscarriage in clinical practice- cohort study. *Acta Obstetrica et Gynecologica Scandinavica*. 2020; 99: 488-493
- [11] Sladkevicius P. Re: Association between ultrasonographic parameters of Cesarean scar defect and outcome of early termination of pregnancy. H.-K. Au, C.-F. Liu, C.-R. Tzeng, and L.-W. Chien. *Ultrasound in Obstetrics & Gynecology*. 2016; 47: 506-510.
- [12] Sonek J, Krantz D, Carmichael J, Downing C, Jessup K, Haidar Z, *et al*. First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. *American Journal of Obstetrics and Gynecology*. 2018; 218: 126.e121-126.e113.
- [13] Guedes-Martins L, Saraiva JP, Gaio AR, Reynolds A, Macedo F, Almeida H. Uterine artery Doppler in the management of early pregnancy loss: a prospective, longitudinal study. *BMC Pregnancy and Childbirth*. 2015; 15: 28.
- [14] Hameed BH. Incomplete miscarriage, expectant versus medical management, and the use of Doppler sonography for patient selection. *Iraqi Journal of Community Medicine*. 2016; 29: 10-15.
- [15] Bao SH, Chigirin N, Hoch V, Ahmed H, Frempong ST, Zhang M, *et al*. Uterine radial artery resistance index predicts reproductive outcome in women with recurrent pregnancy losses and thrombophilia. *BioMed Research International*. 2019; 2019: 8787010.
- [16] Khong SL, Kane SC, Brennecke SP, da Silva Costa F. First-trimester uterine artery Doppler analysis in the prediction of later pregnancy complications. *Disease Markers*. 2015; 2015: 679730.
- [17] Mirza FG, Patki A, Pexman-Fieth C. Dydrogesterone use in early pregnancy. *Gynecological Endocrinology*. 2016; 32: 97-106.
- [18] Kang X, Wang T, He L, Xu H, Liu Z, Zhao A. Effect of low-dose aspirin on midluteal phase uterine artery blood flow in patients with recurrent pregnancy loss. *Journal of Ultrasound in Medicine*. 2016; 35: 2583-2587.
- [19] Trayanov I, Dimitrakova E. Doppler velocimetry of the uterine arteries: an early screening test for miscarriage. *Prilozi*. 2016; 37: 51-56.
- [20] Kane SC, Khong SL, da Silva Costa F. Diagnostic imaging: ultrasound. *Methods in Molecular Biology*. 2018; 1710: 1-8.
- [21] Simcox LE. Identification and validation of ultrasound parameters to predict birthweight and identify late-onset fetal growth restriction. The University of Manchester (United Kingdom). 2019.