Prediction of Spontaneous Abortion Risk by the Use of First Trimester Ultrasound Measurements and Maternal Serum Progesterone Level

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ABSTRACT

Background: Prompt diagnosis of early pregnancy failure is a difficult dilemma. There is no single test currently available which immediately differentiates continuing from non-continuing intrauterine or tubal pregnancy. First-trimester ultrasonography is routinely performed to confirm pregnancy location and assess viability.

Objective: The aim of this study was early detection of spontaneous abortion risk.

Material and methods: This study was conducted in the Department of Obstetrics and Gynecology, Zagzaig University. Sample size was 40 patients. Assuming that mean difference between Group (A) who miscarried and group (B) who continued pregnancy after 20th week in the mean gestational sac diameter 17.9 ± 3.3 and 20.7 ± 3 respectively.

Results: 40 patients with mean age 27.55 ± 3.77 years old ranging from 21 to 37 years. All group were in 7th week of pregnancy. Parity was distributed as 25% were primigravida (PG) and about two third were 1-2 and only 10% had parity >2. MSD, CRL, MSD-CRL and FHR parameters were distributed as 19.98 ± 4.97, 8.42 ± 1.71, 11.56 ± 3.5 and 135.6 ± 15.13 respectively. Women in the abortion group had significantly lower MGSD, CRL, MGSD-CRL ratio and FHR values in comparison with women in the non-abortion group (12.9 ± 2.4 vs. 22.4 ± 2.9, 6.1 ± 0.91 vs. 9.2 ± 1.1, 6.8 ± 1.6 vs. 13.1 ± 2.3 and 115.0 ± 8.2 vs. 142.0 ± 9.6 respectively) with p-value: < 0.001.

Conclusion: Measuring serum progesterone, and first-trimester ultrasound measurements of MGSD, CRL, MGSD/CRL ratio and FHR were good predictors of early pregnancy failure and can be used as a risk assessment model that can predict the risk of early spontaneous abortion.

Keywords: Spontaneous abortion risk, First Trimester Ultrasound, Maternal Serum Progesterone Level

List of abbreviations:CRL, crown-rump length; ELISA, enzyme-linked immunoassay; FHR, fetal heart rate; GSD, gestational sac diameter; MGSD, mean gestational sac diameter; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator characteristic; SD, standard deviation; TVS, transvaginal sonography.

INTRODUCTION

Spontaneous miscarriage is the inevitable termination of pregnancy before 20 weeks of gestation or spontaneous expulsion of fetus below 500g [1]. Spontaneous miscarriage accounts for about 15% of pregnancies. 1% of it is recurrent. More than 80% of abortion occurs in the first 12 weeks of pregnancy; at least half result from chromosomal anomalies [2, 3].

Spontaneous abortion is categorized as threatened, inevitable, incomplete, complete, or missed. Abortion can be further categorized as sporadic or recurrent [3].

Ectopic pregnancy, gestational trophoblastic disease (GTD) and implantation bleeding are differential diagnosis for miscarriage [1].

Progesterone is a C-21 steroid hormone, belongs to a class of hormones called progestogens [2]. Progesterone is produced in adrenal glands, the gonads (specifically after ovulation in the corpus luteum), and the brain.

During pregnancy, it is secreted from corpus luteum and placenta [3].

The maintenance of normal pregnancy up to 7 to 8 weeks of pregnancy is dependent on progesterone synthesis by corpus luteum under the effect of human chorionic gonadotropin, from the 7th week onward the placenta takes over the dominant role of steroid production**.** Progesterone is known to have inhibitory effects on smooth muscle contraction [3]. Serum progesterone measurement is a reliable biochemical test in establishing the diagnosis of early pregnancy failure. Transvaginal ultrasound has revolutionized the diagnosis of early pregnancy as it can detect a pregnancy at an earlier stage, whether it is normal and therefore reassuring, or abnormal and require intervention [3, 4].

Embryonic bradycardia and absence of yolk sac or even a smaller yolk sac diameter than expected for any gestational age are predictors of poor pregnancy outcome during the first 12 weeks [5]. The shape of gestational sac, the echogenicity

of the placenta, the thickness of the trophoblast and the presence of an intrauterine hematoma have all been proposed as sonographic findings associated with early spontaneous miscarriage [3].

The four major criteria of pregnancy failure on which the diagnosis can be reliably made are: the finding of an embryo with a CRL of 6 mm or more on transvaginal ultrasound without heartbeat, the finding of a gestation sac of mean diameter 20 mm or more without a yolk sac, or a sac greater than 25 mm mean sac diameter (MSD) without a visible embryo [6]. **The four minor criteria** for diagnosing pregnancy failure include a thin decidual reaction, a poorly reflective decidual reaction, absence of the double decidual sac sign and low position of the sac in the uterus. Because they are non-specific and unreliable they are not used alone to diagnose pregnancy failure [3].

PATIENTS AND METHODS

Study setting: This study was conducted in the Department of Obstetrics and Gynecology, Zagzaig University.

Study Design: Prospective cohort study.

Sample size: Assuming that the mean gestational sac diameters of Group (A) who miscarried and group (B) who continued pregnancy after 20th week were 17.9 ± 3.3 and 20.7 ± 3 respectively. So, sample size was 40 patients. Sample was calculated using OPEN-EPI program with CI 95% and Power 80%.

Inclusion Criteria:
- Pregnant women in first trimester pregnancy after the 7th week gestation.
- Pregnant women with regular menstrual cycles before pregnancy.
- Pregnant women with sure of date of last menstrual period.
- Pregnant women having ultrasound showing fetal heart beat.

Exclusion criteria:
- Pregnant women with vaginal bleeding during pregnancy.
- Pregnant women suffering from chronic diseases as cardiac or renal or immunity diseases.
- Presence of abnormal findings in ultrasound as ectopic pregnancy or vesicular mole.
- Pregnant women suffering from severe abdominal pain during the pregnancy.
- Pregnant women suffering from recurrent pregnancy loss.

Ethical approval and written informed consent:
An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Operational design:
All the cases in the study were subjected to:
1. Written informed consent before the study.
2. Complete history with special concern to previous medical and surgical treatment.
3. Complete general and abdominal examination.
4. Vaginal U/S for:
   - Confirmation of the gestational age.
   - The measurements includes:
     - Mean gestational sac diameter (MGSD).
     - Crown- rump length (CRL).
     - Embryonic heart rate (EHT).
   - Two measurements were taken and the average between them is calculated.
5. 10 cc of blood was collected for progesterone measurement using Enzyme- linked immunosorbent assay (ELISA).
6. Cases were followed up till the end of the 20th week of pregnancy.

Ultrasonographic measurements:
Ultrasound measurements were carried out transvaginally using SONOACE X4, MEDISON (Deutschland GmbH, Elbestrasse) with a capacity of simultaneous B- mode and M- mode scanning. The transnational sonography was performed using a 6.0 MHz vaginal probe.

All pregnancies were followed up till the completion of the 20th week of pregnancy. The adverse outcome was spontaneous miscarriage occurring before or at the 20th week of gestation as calculated from the onset of normal last menstrual period and corroborated ultrasound data.

Blood Sampling and assay of progesterone:
10 cc of venous blood samples were collected in the first trimester for the measurement of serum progesterone level. The samples were centrifuged at 4,000 rpm for 10 minutes, and the serum was separated and frozen at -70C for assay. The assay was carried out using Enzyme-linked immunosorbent assay technique (ELISA) for measurement of serum progesterone. The assay measures progesterone concentration between 6.0ng/ml to 55.0ng/ml. Measurements of progesterone concentrations were done in batches to minimize analytical variation.

Statistical analysis:
The data were collected, coded and analyzed using SPSS statistical package software.

RESULTS

Age was distributed as 27.55 ± 3.77 with minimum 21 and maximum 37 years old. All groups were in 7th gestational week (Table 1). Parity was distributed as 25% were PG and about two thirds were 1-2 and only 10% had parity > 2. MSD, CRL, MSD-CRL and FHR parameters were distributed as 19.98 ± 4.97, 8.42 ± 1.71, 11.56 ± 3.5 and 135.6 ± 15.13 (Table 2). Progesterone level was distributed as 26.75 ± 5.09 (Table 3). 25.0% of studied group had abortion. Abortion significantly associated with high parity and history of previous abortion as 40% of aborted cases had parity > 2 and history of abortion (Tables 4 & 5).

Table (1): Demographic data distribution among studied group (N=40)

		Age
Age	Mean ± SD	27.55 ± 3.77
	Median (Range)	27.0 (21-37)
Gestational age (GA)	Mean ± SD	7.16 ± 0.21
	Median (Range)	7.0 (7-7.5)

Table (2): Ultrasonography parameters distribution among studied group

MSD	Mean ± SD	19.98 ± 4.97
	Median (Range)	20.5 (10-26)
CRL	Mean ± SD	8.42 ± 1.71
	Median (Range)	8.55 (4.9-11)
MSD-CRL	Mean ± SD	11.56 ± 3.5
	Median (Range)	11.8 (5-16.3)
FHR	Mean ± SD	135.0 ± 15.13
	Median (Range)	138.0 (108-160)

Table (3): Progesterone level distribution among studied group

	Progesterone level
Mean ± SD	26.75 ± 5.09
Median (Range)	29.0 (17-33)

Table (4): Abortion distribution among studied group

		N	%
Abortion	Not	30	75.0
	Aborted	10	25.0
	Total	40	100.0

Table (5): Relation between abortion and basic demographic & clinical characters

			No (N=10)	Aborted (N=10)	X^2	P
Age			26.83±2.94	29.7±5.18	-1.661	0.125
Parity	PG	N	8	2		
		%	26.7%	20.0%		
	1-2	N	22	4	9.15	0.015*
		%	73.3%	40.0%		
	>2	N	0	4		
		%	0.0%	40.0%		
History abortion	No	N	28	6		
		%	93.3%	60.0%		
	Yes	N	2	4	6.53	0.011*
		%	6.7%	40.0%		
Previous labor	PG	N	8	2		
		%	26.7%	20.0%		
	CS	N	11	5	0.56	0.75
		%	36.7%	50.0%		
	Vaginal	N	11	3		
		%	36.7%	30.0%		
Total		N	30	10		
		%	100.0%	100.0%		

Table (6): Comparison between ultrasonography parameters between aborted and non-aborted cases.

	Non-aborted (N=10)	Aborted (N=10)	t	P
MSD	22.35 ± 2.87	12.89 ± 2.4	9.343	0.00**
CRL	9.2 ± 1.06	6.07 ± 0.91	8.331	0.00**
MSD_CRL	13.14 ± 2.32	6.82 ± 1.59	7.957	0.00**
FHR	142.0 ± 9.59	115.0 ± 8.17	8.107	0.00**

Women in the abortion group had significantly lower MGSD, CRL, MGSD-CRL ratio and FHR values in comparison with women in the non-abortion group (12.9 ± 2.4 vs. 22.4 ± 2.9, 6.1 ± 0.91 vs. 9.2 ± 1.1, 6.8 ±1.6 vs. 13.1 ± 2.3 and 115.0 ± 8.2 vs. 142.0 ± 9.6 respectively) with p-value: < 0.001 (Table 6).

DISCUSSION

Pregnancy loss is a common medical problem in reproductive-aged females. Around 25 percent of all women attempting pregnancy experience at least one spontaneous abortion. More than 80 percent of spontaneous abortions are in the first 12 weeks and at least half result from chromosomal anomalies[7].

Serum progesterone measurement had proven helpful in ascertaining if a live intrauterine pregnancy is present. A single serum progesterone measurement of at least 25 ng/ml carries a 97% likelihood for viable intrauterine pregnancy, being more sensitive than two serial hCG measurements. The lowest serum progesterone concentration associated with a viable first trimester pregnancy is 5.1 ng/ml [8].

In order to achieve this aim our study was conducted on 40 pregnant women in the first trimester of pregnancy after the 7th week gestation with viable pregnancy confirmed by ultrasound showing fetal heart rate. All women were subjected to detailed history taking, general examination. Ultrasonography evaluation including MGSD, CRL, MGSD-CRL ratio and FHR. Serum progesterone levels were done for all women at 7th week of pregnancy.

Follow up of pregnancy outcomes of (occurrence of abortion) participating women was done. Our findings showed that the rate of early spontaneous abortion in our study was 25%. (10 pregnant women had spontaneous abortion while the 30 (75%) continued their pregnancy. Similar to our finding is **Alnakash et al.**[9] who found that 21.25% of women had developed miscarriage in their study on 80 women with threatened miscarriage.

The mean age of participating pregnant women in our study was 27.6 ± 3.8 ranging between 21 – 37 years old. Further analysis according to occurrence of spontaneous abortion was done and our results showed that the women with spontaneous abortion were significantly elder than those who continued their pregnancy (29.7 ± 5.18 vs 26.83 ± 2.94 with p-value: 0.035).

Miscarriage had a direct association with history of previous spontaneous abortion and parity. History of spontaneous abortion significantly increased the risk of miscarriage, while a history of previous live birth considerably decreased the risk. They explained that patients who experienced primary miscarriage are more likely to have uterine anomalies, which are a risk factor for miscarriage [10]. **El-Mekkawi et al.** [11] is in agreement with our findings regarding the point of parity as they reported that in their study there was women in group 1 (abortion group) had a statistical higher parity compared to those of group 2 (non-abortion group) with p-value: < 0.001. Our results disagree with **Al-Mohamady et al.** [8] who reported in their study on 100 pregnant patients with vaginal bleeding that 20 cases ended by miscarriage (group 1) and 80 cases (group 2) continued till 20 weeks of gestation. No statistical significant differences were found between both groups as regards maternal age, parity and the number of previous miscarriages.

All participating women in our study were subjected to ultrasonography evaluation to assess the MGSD, CRL, MGSD-CRL ratio and FHR. Our results showed that their values were 22.35 ± 2.87, 9.2 ± 1.06, 13.14 ± 2.32 and 142.0 ± 9.59 in the non-abortion group respectively. Further statistical analysis showed that women in the abortion group had significantly lower MGSD, CRL, MGSD-CRL ratio and FHR values in comparison with women in the non-abortion group (12.9 ± 2.4 vs. 22.4 ± 2.9, 6.1 ± 0.91 vs. 9.2 ± 1.1, 6.8 ±1.6 vs. 13.1 ± 2.3 and 115.0 ± 8.2 vs. 142.0 ± 9.6 respectively) with p-value: < 0.001. While in the study done by **Maged and Al-Mostafa** [7], they reported that the women in aborted group had significantly lower FHR and CRL and insignificantly lower MGSD compared to those in the continued an control groups with p-value: <0.05, <0.05 and > 0.05 respectively. **Altay et al.** [12] reported that for MGSD–CRL ratio, at cutoff point "threshold level" < 1, MGSD–CRL ratio had 42.10% positive predictive value, and 95.78% negative predictive value with 66.67% sensitivity and 89.21% specificity. Regarding FHR, our results are in agreement with **Datta and Raut** [13] who reported that the optimum cutoff value of FHR for the continuation of pregnancy was 128 bpm. And found all pregnancies with FHR below 80 bpm resulted in spontaneous abortion in their study. They found that coefficient of determination (R^2) for FHR below 130 bpm was 0.267. Therefore, for every 10- bpm decrease in FHR below 130, the risk of abortion increased by 26.7%.

Regarding serum progesterone level, our results showed that the women in the abortion group had

significantly lower serum progesterone level compared to those in the non-abortion group (29.3 ± 2.3 vs. 19.0 ± 2.6) with p-value: <0.001. Our result is in agreement with **Maged and Al-Mostafa** [7] who reported that there was a statistically significant difference between the women diagnosed as threatened abortion cases who ended their pregnancy in abortion and those with the diagnosis of threatened abortion who completed their pregnancy and those with a normal pregnancy regarding progesterone level with p-value: < 0.05. In the study done by **Al-Mohamady et al.** [8] they reported that using a ROC curve for progesterone level in predicting the outcome of pregnancy in threatened miscarriage cases, the cut-off limit of 11.5 ng/ml of progesterone level achieved sensitivity of 97.5 % and specificity of 100%. In the study done by **El-Mekkawi et al.** [11] serum progesterone level at cutoff point 27 ng/ml had 63.0% sensitivity and 56.0% specificity in prediction of spontaneous miscarriage.

Serum progesterone plays a crucial role in the maintenance of pregnancy via the inhibition of oxytocin-induced myometrial activity and prostaglandin excitation. Despite these observations, because of the large biological variability of serum progesterone in early pregnancy, choosing a discriminatory value to predict viable and non-viable pregnancy is difficult [13].

Statistical correlation between FHR and progesterone level and other ultrasonographic parameters were studied and our results showed that both FHR and progesterone level had a strong significant direct correlation with MGSD, CRL and MGSD-CRL ratio with p-value: < 0.001.

CONCLUSION

Measuring serum progesterone, and first-trimester ultrasound measurements of MGSD, CRL, MGSD/CRL ratio and FHR are good predictors of early pregnancy failure and can be used as a risk assessment model that can predict the risk of early spontaneous abortion.

We recommended that: Routine first-trimester ultrasonography parameters including MGSD, CRL, MGSD/CRL ratio and FHR should be recorded to confirm pregnancy. Serum progesterone level should be measured in the first trimester for early detection of early spontaneous abortion especially in at risk pregnant women. Further studies on large population especially on women with high risk pregnancy should be conducted to confirm our result and establishment of more reliable model that can help the risk of early spontaneous abortion.

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