Ultrasonographic Estimation of Gestational Sac Diameter in Normal Pregnancy, Missed Abortion and Blighted Ovum in Early Pregnancy and Its Sequel

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ABSTRACT

Background: Missed abortion and blighted ovum are associated with maternal morbidity and mortality, so early and accurate diagnosis means early management and less complications.

Objective: To compare gestational sac size between normal pregnancy and missed abortion and blighted ovum to determine at what gestational age differences in gestational sac size become evident. Also, to see whether it is possible that we can use it as a parameter to differentiate between normal and abnormal pregnancies, especially at early stages, when diagnosis of failed pregnancies can be difficult.

Methods: A prospective observational study at Department of Gynecology and Obstetrics at Al-Yarmouk Teaching Hospital for a period of one year from the first May 2015 to the first of May 2016 on 113 women with early pregnancy were included in this study. Two dimensional abdominal ultrasound of the gestational sac size was done and follow up weekly starting at 6 week until 9^{+6} weeks by serial ultrasound measurement of the sac size and its sequel, and comparison was made between the subgroups (normal early pregnancy, missed abortion, blighted ovum).

Results: There were 56 normal early pregnancies 46 missed abortions and 11 blighted ovum. Gestational sac size was significantly larger in normal pregnancies compared to missed abortion and blighted ovum, this difference started at 7 week between normal pregnancy and missed abortion: 23.3±2.2 cm^2 and 20.5±3.2 cm^2, respectively ($p < 0.001$), and 8 week between normal pregnancy and blighted ovum: 30.9±2 cm^2 and 26.4±3.5 cm^2, respectively ($p < 0.001$). And the differences keep increasing during the ninth and tenth weeks of gestation.

Conclusion: Gestational sac size in missed abortion and anembryonic pregnancies is significantly smaller than in normal pregnancies, starting at 7 weeks for missed abortion and 8 weeks for blighted ovum.

Keywords: Gestational sac size, Missed abortion, Blighted ovum, Normal pregnancy; Two-dimensional ultrasound.

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Before widespread use of ultrasonography, the term missed abortion was given to pregnancies with no uterine growth over a prolonged period of time, typically 6 weeks[1,2]. Ultrasound plays an important role in women who have unsure dates of their last menstrual period (LMP) or had used hormonal contraception, or been pregnant or breastfed in the last 3 months of their current pregnancy.

Improved access to early pregnancy units and increasing awareness amongst women of their choices in the management of early pregnancy problems has led to an increasing demand for more conservative management of early miscarriage[3,4].

Demonstration of a gestation sac within the uterus is the earliest ultrasonic confirmation of an intrauterine pregnancy. It is a structure that surrounds the embryo and can be seen even before the embryo is visible. Thickening of the endometrium might be recognized prior to this but

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cannot be taken as diagnostic of pregnancy[5-7].

From a clinical standpoint, abortion can be classified a number of ways: Threatened, inevitable, incomplete, complete, recurrent, and missed[8-10].

The diagnosis of missed abortion is determined by the ultrasound identification of an embryo/fetus without any heart activity. It is relatively easy to make this diagnosis by means of transvaginal color Doppler ultrasound[11]. The main parameter is the absence of the heart beats and the lack of color flow signals at its expected position after the 6th gestational week. If the fetal pole is less than 8mm with no cardiac activity identified within 30 seconds, then the diagnosis of pregnancy of uncertain viability may be made[12].

A repeat ultrasound examination should be arranged after 7-10 days to clarify the diagnosis. An ultrasound diagnosis of fetal demise may be made when there is no fetal heart in a fetus with fetal pole >5mm when using transvaginal ultrasound. The area of the fetal heart should be observed for a prolonged period of at least 30 seconds to ensure that there is no cardiac activity. With the aid of sensitive color Doppler equipment, it is possible to demonstrate two types of blood flow Velocity waveforms from the intervillous space 31 (pulsatile arterial-like and continuous venous-like patterns) in both, normal and abnormal early pregnancies. In long-standing demise, the cessation of the embryonic portion of placental circulation leaves the fluid pumping action of the trophoblast unaffected, as it remains nourished by the maternal side of circulation[13].

The use of transvaginal ultrasound should be encouraged as better visualization is nearly always possible[14]. Different cutoffs for diagnosing miscarriage apply when using transabdominal ultrasound. If the mean gestational sac is smaller than expected, the possibility of incorrect dates should always be considered, especially when there is no pain or vaginal bleeding. In these circumstances, a repeat transvaginal scan should be arranged after 7-10 days. It is important to listen carefully to the views of the woman, particularly in circumstances where she has had a prior pregnancy[15].

Sonographic diagnosis of embryonic demise can be made when there is no cardiac activity in an embryo greater than 5 mm by transvaginal ultrasound or 9 mm by abdominal ultrasound[16]. Given the possibility of measurement error, it is prudent to allow an additional 1 to 2 mm in gestational sac measurement before considering intervention[17]. If the gestational sac is smaller than expected, under these circumstances, a repeat transvaginal scan should be arranged after a 1-week interval[18].

Blighted ovum (anembryonic pregnancy) refers to a gestational sac in which the embryo either failed to develop or died at a stage too early to be visualized. Advances in transvaginal sonography allow us to detect this kind of abnormality at a mean sac diameter of 1.5 cm[19]. If on transvaginal ultrasound, the mean gestational sac diameter is less than 20mm with no yolk sac or embryo. And by transabdominal ultrasound if the mean gestational sac diameter is >25mm in the absence of a yolk sac or embryo. To confirm the diagnosis, these findings should be correlated with other clinical and sonographic data including the presence of a yolk sac[20]. The diagnosis of a blighted ovum is in 100% of cases by 2D real-time ultrasonography examinations when performed a week apart after absence of embryo development has been confirmed[21].

There are certain ultrasound features which predict but are not diagnostic of early pregnancy failure. These include a fetal heart rate of less than 85 beats per minute at greater than 7 weeks' gestation, a small sac size relative to the embryo (difference of less than 5 mm between gestation sac and crown rump length)[22,23].

——————————Methods

This is a prospective observational study carried out at the Department of Obstetrics and Gynecology at Al-Yarmouk teaching hospital, Baghdad, Iraq. The study was conducted over a period of one year, from the first of May 2015 to the first of May 2016 after approval of the study protocol by the scientific counsel of obstetrics and gynecology of Arab Board for Medical Specialization

The study was started with one hundred fifty women only one hundred thirteen women conducted to the end of the study some ended with complete or incomplete miscarriages others were lost to follow-up. The criteria for inclusions in this study were; natural conception, first attendance in the index pregnancy, history of positive pregnancy test, gestational age from the first day of the last menstrual period (LMP) of 6 weeks and intrauterine pregnancy. Women with gestational age less than 5 weeks or more than 12 weeks, ectopic pregnancy, molar pregnancy and multiple gestations were excluded.

Verbal consent was obtained from each woman included in this study. The patients were collected from outpatient clinic in the obstetrics and gynecology department of Al-Yarmouk Teaching Hospital. The department is open all days a week and receives self-referrals and from other health care practitioners. Women attended for a number of reasons, including abdominal pain, uncertain menstrual dates, maternal anxiety or a history of a previous early pregnancy complication. Questionnaire format was done to evaluate many of the dependent variables such as patient`s age, gravidity and parity, past obstetrical, gynecological, medical and surgical history. Patients underwent general, systemic and obstetrical examination. Gestational age was assessed by LMP and confirmed by ultrasonography.

Two-dimensional ultrasound assessment of gestational sac diameter: Transabdominal ultrasound was performed with Voluson 730 system equipped with a 5 MHz curved array transducer. By an experienced operator, two dimensional ultrasound examinations were done. Mean sac diameter is calculated from the following equation:

Mean sac diameter (cm) = [L (cm) + AP (cm) + T (cm)]/3

The maximum longitudinal axis (L) of the sac was obtained. We obtained the section demonstrating the maximum transverse diameter (T) of the sac. The maximum anteroposterior diameter (AP) was measured from either the longitudinal or transverse section because it is common to both views, (Figure 1)[19].

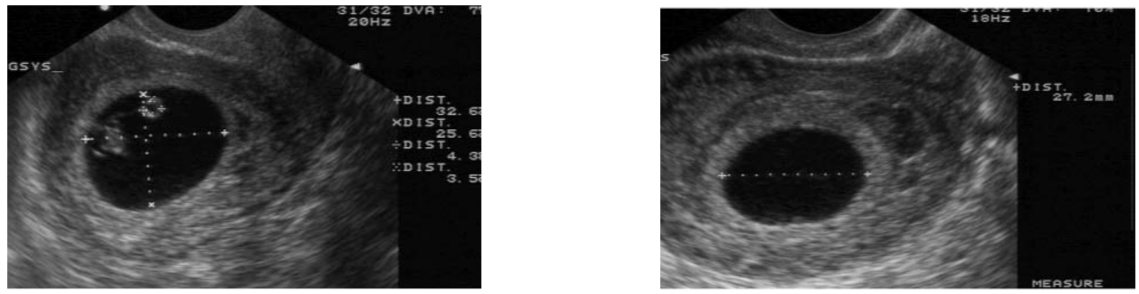

Figure 1: Longitudinal section of the uterus demonstrating the maximum longitudinal diameter (L) of the gestation sac. B. Transverse section of the uterus demonstrating the maximum transverse (T) diameter of the gestation sac. Note that the AP diameter is common to both views. The mean gestation sac volume is equivalent to a gestational age of 5 weeks 4 days. Note the echogenic appearance and the thickness of the wall of the sac [19].

Also, the crown rump length (CRL) was measured. Missed abortion was diagnosed when a fetal pole was at least 5 mm without heart activity in at least two consecutive scans at least 24 hours apart. Anembryonic pregnancy was diagnosed when at least gestational sac diameter of 20mm or more without a yolk sac or fetal pole. Viable pregnancy was confirmed after visualization of cardiac activity and followed up until 10 weeks.

The gestational sac measurement was taken starting at 6 weeks and repeated weekly till 9 week +6 days. And pregnancies were followed up, some continued as viable early pregnancy, other as missed miscarriage and blighted ovum, (incomplete and complete miscarriages were excluded from the final analysis).

The data entry and management was done via STATA program (ver. 13, 2014). The categorical data presented as frequency and percentages, while continuous data represent using mean and standard deviation. Independent t-test was used to compare average crown-rump length between group with viable fetus and those with missed abortion.

Analysis of Variances (ANOVA) both regular and repeated measures ANOVA was used accordingly for comparison of average gestational sac size among study groups along the time of the study as well as comparison of average crown-rump length along the time of the study. LSD post-hoc tests were used to compare the average differences between the variables. P-value of 0.05 or less considered significant.

Results

The current study included 113 women, about half of them were having viable fetuses while 46 (40.7%) of them had missed abortion and one-tenth of the patients' pregnancies found to be blighted ovum, (Table 1).

In comparison of the main parameters of the studied women, the results showed that; women with blighted ovum were significantly older than other groups (p= 0.003). There was no significant age difference between viable pregnancy and missed abortion, (Tables 2 and 3).

Women with blighted ovum appeared to have had abortions more frequently than other groups with significant differences (p<0.001). The difference in previous abortion between normal pregnancy group and missed abortion group was not significant. Neither gravidity nor parity showed significant differences according to the study groups, (Tables 2 and 3).

Both maternal age and the groups themselves found to affects significantly the size of gestational sac in the association with the time elapsed during pregnancy (p= 0.001 and p<0.001) subsequently. Moreover, partial eta square value (power of effect) for maternal age was weak 9.6% in comparison to 47% for different group, thus sac size majorly different due to the defects themselves (missed abortion or blighted ovum), (Table 3).

The differences described above are thoroughly explained in table 4 below and it is clear that differences between the study groups with sac size increment in the normal group and exceeded that in others. Also, we can see the steady and significant increase in the average of sac size with the gestational age, (Table 4).

Only groups in association with the time have significant effect (p<0.001) with 77% impact on the crown rump length. Age of the mother appeared to have no significant effect on the crown rump length, (Table 6).

Table 1: The distribution of the included patients, according to the study groups.

Study groups	Frequency	Percent
Viable pregnancy	56	49.6
Missed abortion	46	40.7
Blighted ovum	11	9.7
Total	113	100.0

Table 2: The average of main parameters of the studied women.

Variables	Viable pregnancy (N=56)	Missed abortion (N=46)	Blighted ovum (N=11)	p-value
Age (years)	28.1±7.3	31.8±7.2	35.4±6.2	0.003*
Gravida	3.1±1.7	3.5±2.3	3.6±1.1	0.574 ns
Para	1.9±1.5	1.5±1.7	1.4±0.5	0.418 ns
Abortion	0.3±0.5	1±0.7	1.2±1.2	<0.001*
*Significant at 0.05 level by ANOVA test				

Table 3: The mean differences between the study groups (LSD post-hoc test).

Dependent Variable	(I) Groups	(J) Groups	Mean Difference (I-J)	p-value
Age (years)	Viable pregnancy	Missed abortion	-3.6	0.013*
		Blighted ovum	-7.3	0.003*
	Missed abortion	Blighted ovum	-3.7	0.131
Abortion	Viable pregnancy	Missed abortion	-0.7	<0.001*
		Blighted ovum	-0.9	<0.001*
	Missed abortion	Blighted ovum	-0.2	0.376
* The mean difference is significant at the 0.05 level.				

Table 4: The test of between-Subjects Effects shows the effective factors on gestational sac variation with time.

Effect	Type III Sum of Squares	df	Mean Square	F	p-value	Partial Eta Squared
Age	302.99	1	302.99	11.696	0.001*	0.096
Groups	2524.56	2	1262.28	48.726	<0.001*	0.47
*Significant at 0.05 by repeated ANOVA test						

Table 5: The LSD post-hoc test comparison of gestational sac size among study groups according to different times in early pregnancy.

(I) Groups	(J) Groups	Mean Difference (I-J)	p-value
Viable pregnancy	Missed abortion	5.083	<0.001*
	Blighted ovum	2.512	0.007*
Missed abortion	Blighted ovum	-2.572	0.005*
(I) Time	(J) Time	Mean Difference (I-J)	p-value
6wks - 6wks+6d	7wks - 7wks+6d	-6.74	<0.001*
	8wks - 8wks+6d	-12.36	<0.001*
	9wks - 9wks+6d	-16.05	<0.001*
7wks - 7wks+6d	8wks - 8wks+6d	-5.62	<0.001*
	9wks - 9wks+6d	-9.31	<0.001*
8wks - 8wks+6d	9wks - 9wks+6d	-3.69	<0.001*
* The mean difference is significant at the 0.05 level.			

Table 6: The test of between-Subjects Effects shows the effective factors on crown rump variation with time.

Effect	Type III Sum of Squares	df	Mean Square	F	p-value	Partial Eta Squared
Age	18.264	1	18.264	3.413	0.068	0.033
Groups	1811.871	1	1811.871	338.614	<0.001*	0.77
*Significant at 0.05 by repeated ANOVA test						

Discussion

Many problems can occur during pregnancy. The cause of a miscarriage can reside in the person's genes, anatomy, endocrine system, immune system, blood-clotting system, or environment, but in many cases no cause can be found. The experience can be painful for the couple[24]. So the earliest the diagnosis of pregnancy failure the best for the couples to overcome the emotions and return to their normal life.

One hundred thirteen patients included in this study 11 blighted ovum 46 missed abortion and 56 normal pregnancies. In the present study participants' there is increase in mean maternal age in blighted ovum compared to other groups (P=0.003), There was no significant age difference between viable pregnancy and missed abortion. These results agree with Blohm *et al*[25] study, a prospective longitudinal population – based study of clinical miscarriage according to maternal age in Swedish women was as follows: 20-24 years 13.5%, 25, 25-29 years 12.3%, 30-34 years 10.3%, and 35-39 years 17.5%.

Anne *et al* [26], in Denmark, they studied maternal age and fetal loss: a population based register linkage study where their research database of parity was established with data from this registration system, including information on all live births to women born between 1 April 1935 and 31 March 1978. They found that the risk of a spontaneous abortion was 8.9% in women aged 20-24 years and 74.7% in those aged 45 years or more. High maternal age was a significant risk factor for spontaneous abortion irrespective of the number of previous miscarriages, parity, or calendar period.

These result agrees with another study for Makrydimas and Sebire's study[27], in Department of Obstetrics and Gynaecology, Ioannina, they studied the relation of demographic data and ultrasound findings at the time of the initial assessment to subsequent fetal loss was examined, The findings of this study demonstrate that the incidence of miscarriage increases with maternal age, from about 4% for those aged less than 20 years to about 20% for those aged more than 35 years.

Alnakash *et al* study[28], conducted in Al-Elwiya Maternity Teaching hospital Bagdad, Iraq. This study showed an increase risk to fetal demise with increasing maternal age, 41.18% of them had miscarriage at age 36-39 years which was highly significant (P=0.03).

Rates of pregnancy loss are higher in women with advanced maternal age; the risk rises with maternal age, whether or not the fetus is normal and that in older women, oocyte tend to have more chromosomal abnormalities and the endometrium is less receptive[29]. Also, ovarian aging which changes the rate of meiotic errors in the oocyte[30].

Regarding parity and gravidity our study found no association between failed pregnancy (missed abortion, blighted ovum) and higher gravidity or parity, while in a previous study carried out by Shuaib and Alharazi[29], in Yemen in 2011 among 107 patients and aimed to compare the medical and surgical methods for the treatment of missed miscarriage, this study showed that there was no significant difference in body mass index, neither in

the parity nor gravidity of the participants, also they stated that women with previous history of missed miscarriage did not have a significant chance to have another one, which are similar to our finding regarding the effect of gravidity and parity and disagree regarding history of previous miscarriage.

The present study disagrees in results with a case-control study that carried out during the period from October 2008 till September 2009 in Basrah, Iraq among 182 (91 were having missed miscarriage and 91 was with healthy pregnancy) by Sadoon and Hosney[31], which was designed to evaluate the occurrence of acute human parvovirus B19 infection among pregnant women and its association with spontaneous abortion, they reported that; miscarriage was significantly higher among women of higher gravidity and higher parity (P<0.05).

Also, it disagrees with previous study conducted in Iraq at Al-Yarmouk Teaching Hospital in Baghdad city between November 2008 and December 2009, by Akram. During this period a total of 67 patient with missed abortion were attended the outpatient clinic, of them only 33 patients were collected and enrolled into the study which aimed to compare for the treatment outcomes of women complained of early missed miscarriage; the study found that; both multigravida and multipara were significantly higher among the miscarriage group of no response to treatment in comparison to the control group (P=0.0059) for both, and that women with past history of miscarriage were significantly more liable to have another one[32]. While the history of previous miscarriage showed significant association with missed abortion and blighted ovum, which agreed with our study at this point.

Regarding history of previous miscarriage in the current study, women with blighted ovum appeared to have had abortions more frequently than other groups with significant differences (P<0.001). The difference in previous abortion between normal pregnancy group and missed abortion group was not significant. Two studies (Shuaib & Alharazi and Akram) gave results agreeing with ours regarding this subject [29,32].

In this study we also compared the gestational sac sizes among the study groups. At the 7th week of the sac size of the missed abortion group was significantly lower than other groups (P=0.003). These differences appeared clearly and more significantly as the gestational age increase (P<0.001); but, since the eighth week the sac size in viable pregnancy group exceeded that in blighted ovum and the difference keep increasing during the ninth and tenth weeks of gestation.

In Odeh *et al* study[33], in department of obstetrics and gynecology, Israel. They showed the difference in GSV between the groups week by week, GSV in missed abortions or anembryonic pregnancies became significantly smaller beginning at 7 weeks of gestation.

Acharya and Morgan study[34], were they evaluated that GSV measurement did not predict the outcome of expectant management of missed abortion; however, the GSV as measured by Acharya and Morgan was similar to our results (9.7±8.9 cm^3 and 8.04±10.5 cm^3, respectively).

In early pregnancy failure, the contribution of the embryo and the trophoblast is expected to decrease; however, the stage at which this decrease begins is unknown. Since the difference in gestational sac size become evident at 7 weeks we suggest that it may be the time of diminished production of amniotic fluid.

In the current study Crown rump length showed no significant difference between normal group and missed abortion at the 7th week of gestation. The difference started to be significant from the 8th week and above (P<0.001), because the fetuses in normal group keep growing steadily in reverse to those from missed abortion.

Results of Odeh *et al* study[33], agrees with ours, the CRL was significantly

different between the groups (2.39±1.42 cm in normal pregnancies versus 0.98±0.92 cm in missed abortions (P<0.001)).

In several studies (Bromly *et al*[35] and Dicky *et al*[36]), a small GS was associated with high pregnancy loss rate, suggesting that reduction of amniotic fluid production precedes fetal demise.

In conclusion; ultrasound evaluation of gestational sac size in early pregnancy is noninvasive clinical tool that may predict early pregnancy failure in early stages were diagnosis of missed abortion is still questionable, Where the sac size may be used as predictive value for the early prediction of the loss but need follow-up. It was found that gestational sac size in missed abortion and anembryonic pregnancies is significantly smaller than in normal pregnancies, starting at 7 weeks for missed miscarriage and 8 weeks for blighted ovum.

It is recommended for need of early report of pregnancy for antenatal care and the use of early ultrasound as soon as pregnancy diagnosed to confirm the viability status of the fetus as the earlier the diagnosis of pregnancy failure the earlier the management. There is a need to confirm the results obtained with larger studies in the future.

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