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The Value of Current Triple Ultrasonographic Markers in Cases of unexplained Early Recurrent Miscarriage

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Abstract

Introduction: Recurrent miscarriage is the loss of three or more consecutive pregnancies before 20 weeks or fetal weight of 500 grams. Seventy five percent of these cases occur in the first trimester. Several studies investigated ultrasonographic landmarks to try to differentiate between normal and abnormal pregnancies.

Objective: Differentiate between normal and abnormal pregnancy using three ultrasound markers: fetal heart rate, gestational and yolk sac diameters.

Study design: Prospective observational study.

Patients and methods: One hundred and sixty patients carrying a singleton intrauterine pregnancy within the first seven weeks of pregnancy with three or more unexplained consecutive pregnancy loss did weekly serial transvaginal ultrasound from 5 until 13 weeks the latter gestation was performed by transabdominal ultrasound to measure gestational and yolk sac diameters and fetal heart rate.

Results: There was a significant difference in fetal heart rate, gestational and yolk sac diameters on weekly basis as pregnancy advances. There was a significant difference in fetal heart rate and yolk sac diameter between normal and abnormal pregnancies ($P < 0.001$), however, this was insignificant as regards gestational sac diameter.

Conclusion: Multiple ultrasound parameters with serial examinations are better than a single parameter or examination in predicting pregnancy outcome in cases with recurrent unexplained first trimester miscarriage.

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Kyewords: Ultrasound markers; Unexplained; Recurrent early miscarriage

Abbreviations: YS = Yolk sac, GS = Gestational, HR = Fetal Heart Rate, YSD = Yolk Sac Diameter GSD = Gestational Sac Diameters, LMP = Last Menstrual Period

Introduction

Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies before 20 weeks or fetal weight of 500 grams, however, many authors start their evaluation after two consecutive losses[1]. Seventy five percent of these cases occur in the first trimester and twenty five percent occur in the second trimester[2].

Precise differentiation between normal and abnormal pregnancy during early gestation is a clinical challenge[3]. Several studies investigated ultrasonographic early gestational landmarks to try to differentiate between normal and abnormal pregnancies as Yolk Sac (YS), Gestational Sac (GS), fetal pole or Fetal Heart Rate (FHR)[4].

Due to the discrepancy in determining a cut-off value for gestational sac diameter to differentiate a normal from an abnormal pregnancy we chose the combination of three ultrasound markers (mean gestational sac diameter, yolk sac and fetal heart rate) for this purpose in our study.

Patients and methods

This prospective observational study was done in 6th October and Al-Azhar University hospitals from January 2014 to February 2015. The Ethical Committee of Faculty of medicine Al-Azhar University approved this study. Two Hundred and twelve cases with unexplained two or more consecutive pregnancy loss who carried a singleton intrauterine pregnancy within the first seven weeks of pregnancy and were sure of dates were selected for this study while, patients presenting after 7 weeks, those with symptoms of threatened miscarriage, those with multi-fetal pregnancies or a known cause of recurrent miscarriage (Previously found diagnostic cause for RM) were excluded from the study, and investigations of the latter cause was done before the patients were enrolled in the study. The diagnostic workup which was done for women with RM according to our units protocol as follows; pre-pregnancy screen for antiphospholipid antibodies, with two positive tests at least 12 weeks apart for either lupus anti coagulant or anticardiolipin antibodies, previously done cytogenetic analysis of the third miscarriage, previously done pelvic ultrasound to assess uterine anatomy, and previously screened for inherited thrombophilia including factor V Leiden, prothrombin gene mutation and protein S deficiency.Informed consent was obtained from all patients for enrollment in the study. Nineteen cases refused to do transvaginal ultrasound and thirty three cases were lost during follow-up and one hundred and sixty cases continued the study to the end. All cases were subjected to detailed history, physical examination and routine pregnancy investigations as ABO & Rh grouping, full blood count and urine analysis, in addition to weekly serial transvaginal ultrasound from 5 - 7 weeks until 13 weeks the latter gestation was performed by transabdominal ultrasound. The ultrasound machine used was SonaAce 1500 manufactured by Medison 2002 and equipped with 6.5 MHz vaginal probe and 3.5 MHz convex abdominal probe. The GSD and YSD were measured in the B-mode by putting the calipers on the innermost limits of their internal diameters perpendicularly and the mean was taken while, the FHR was measured in the M-mode by recording the time interval of at least three waves which informs us about the number of fetal heart beats per minute and the values were registered in the patient's file. All women were instructed to return after one week for re-scan or to come at once if vaginal bleeding or pelvic pain occurred. If no complications occurred, the cases were instructed to comeback at 6th, 7th, 9th, 11th and 13th week which is the end-point of the study.

The cases of the study included 6 groups:

1) Normal values for GSD. 2) Small for date GSD.
3) Normal values of YSD. 4) Abnormal values for YSD.
5) Normal values of FHR. 6) Abnormal values for FHR.

Normal values for GSD, YSD and FHR used according to measurement tables done by Campbell., *et al* 1985[5], which is our unit's protocol.

Statistical methods

Data were described in terms of frequency (number of cases), minimum diameter, maximum diameter, mean diameter, median mode and Standard Deviation (SD).

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS®) for Windows®) VERSION 15.0. Normally distributed numerical data were presented as mean and SD. Between group differences were compared using the unpaired student's t-test. Categorical data were presented as number and percentage, while inter-group differences were compared using the Pearson chi square test (for nominal data) or the chi square test for trends (for ordinal data). Validity of study parameters was evaluated in terms of accuracy, which was calculated by sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV). P value was considered significant if 0.05 or less. Regression analysis between GSD, YSD and FHR and the relation between them in all groups of the study either in normal or abnormal outcomes were analyzed. GSD, YSD and FHR were analyzed to see if they lie within 2 SD above or below the mean normal outcome group and above or below 2 SD in abnormal outcome group. GSD, YSD, FHR, LMP and maternal age will be statistically analyzed to test if the difference between the subgroups of each variable is of value in predicting first trimester pregnancy outcome.

Results

According to the outcome in this study cases were classified into 2 groups:

Normal outcome group in which Pregnancy continued successfully including 112 cases (70% of total cases), and abnormal outcome group in which miscarriage occurred which includes 48 cases (30% of total cases) 36 of which had absent yolk sac while the remaining 12 cases had measurable yolk sac.

The study has 3 variables which are GSD, YSD and FHR while secondary outcomes included maternal and gestational age.

The mean age of the normal cases was 24.86 +/- 4.46 as standard deviation and the mean age for the abnormal cases was 31.50 +/- 6.37 standard deviation (P-value < 0.001).

As regards Parity in the normal group we had 32 cases who were nullipara (28.57%), 20 cases who delivered once (17.86%), 32 cases who delivered twice (28.57%), 20 cases who delivered 3 times (17.86%), 8 cases who delivered 4 times (7.14%) and none of the cases delivered 5 times. As regards the abnormal group we had 20 cases who were nullipara (41.67%), 16 cases who delivered once (33.33%), 4 cases who delivered twice (8.33%), two cases who delivered 3 times (4.17%), another 2 cases who delivered 4 times (4.17%) and 4 cases who delivered 5 times (8.33%). (P-value = 0.186).

The mean and standard deviation of hemoglobin level was 10.72 +/- 1.64 for the normal cases and 8.91 +/- 2.27 in the abnormal cases (P-value = 0.01).

As regards the pregnancy outcome for normal group, we had 5 cases (4.46%) who had fetal growth restriction, which had within normal measurements in the first trimester scans.

Discussion

Medical intervention in patients with threatened miscarriage can only start when there is certainty about pregnancy failure so diagnostic tests performed in the first trimester should be 100% specific with the highest possible sensitivity[6]. The main aim of this study was to formulate ultrasound criteria to differentiate between normal and abnormal first trimester pregnancies to be prospectively applied in all uneventful pregnancies. The number of cases with fetal growth restriction (4.46%)

were not large enough for comparison of ultrasound data.

All implanted pregnancies appear to start from the same baseline, however, follow-up of the gestational sac diameter showed that abnormal pregnancies had decline growth curves starting from 5 weeks of gestation when the sac diameter exceeded 3 - 4 mm, therefore, it is expected that actively dividing embryonic cells are more likely to be compromised[7], with trisomy 16 and triploidies being a more likely cause to abnormal gestational sac growth before 9 weeks than other chromosomal anomalies[8]. Although the current study found a significant difference in the mean gestational sac diameter during weekly follow-up (Table 1) no significant difference between the mean diameter of normal and abnormal cases were found (Table 2).

Table 1: Changes in gestational and yolk sac diameters in all patients throughout the study.

Gestational	Gestational sac diameter(GSD)			Difference		Paired	t-test
Age	Range	Mean	SD	Mean	SD	t	P-value
W5	8.5 - 18	10.84	+/-2.38				
W6	9.54 - 26.11	16.71	+/-3.32	-5.87	2.86	-12.99	< 0.001
W7	9.91 - 48	24.38	+/-7.44	-13.54	6.96	-12.31	< 0.001
W9	10.8 - 65.22	35.31	+/-11.9	-24.47	11.77	-13.15	< 0.001
W11	10.59 - 81.11	45.86	+/- 18.2	-35.02	18.14	-12.21	< 0.001
W13	21 – 88.19	57.45	+/- 23.21	-47.11	24.13	-11.38	< 0.001
Gestational	YSD	YSD	YSD	Diff.	Diff.	Paired	t-test
W5	0 - 5.93	2.16	+/- 1.33				
W6	0 - 6.60	2.67	+/- 1.60	-0.50	0.55	-5.80	< 0.001
W7	0 - 7.10	3.20	+/-2.01	-1.03	1.02	-6.39	< 0.001
W9	0 - 8.00	3.44	+/-2.26	-1.27	1.22	-6.60	< 0.001
W11	0 - 8.11	3.23	+/- 2.93	-1.07	2.18	-3.10	< 0.001
W13	0 - 0.00	0.00	+/- 0.00	2.13	1.43	8.69	< 0.001

Table 2: Differences between normal and abnormal cases of the study as regards fetal heart rate, gestational and yolk sac diameters during 5th, 6th, 7th, 9th, 11th and 13th week of gestation.

GSD	Normal		Abnormal		T-	test
	Mean	SD	Mean	SD	t	P-value
W5	10.7	+/- 2.29	11.16	+/- 2.67	-0.54	0.59
W6	16.93	+/- 3.62	16.19	+/- 2.56	0.64	0.52
W7	25.31	+/- 7.44	22.22	+/- 7.29	1.21	0.23
W9	36.8	+/- 11.01	31.82	+/- 13.62	1.22	0.23
W11	48.49	+/- 16.47	39.71	+/- 21.2	1.42	0.17
W13	60.59	20	50.88	+/- 28.76	1.15	0.26
YSD						
W5	2.70	+/- 1.02	0.91	+/- 1.14	4.94	< 0.001
W6	3.37	+/- 1.15	1.03	+/- 1.29	5.70	< 0.001
W7	4.10	+/- 1.49	1.09	+/- 1.36	6.01	< 0.001
W9	4.46	+/- 1.74	1.04	+/- 1.30	6.08	< 0.001
W11	4.29	+/- 2.84	0.78	+/- 1.16	4.11	< 0.001
W13	0.00	+/- 0.00	0.00	+/- 0.00		
Fetal Heart rate						
Week 5	80.68	+/- 13.34	35.08	+/- 43.65	5.08	< 0.001
Week 6	92.64	+/- 20.67	35.00	+/- 43.43	5.73	< 0.001
Week 7	119.71	+/- 17.05	40.83	+/- 51.57	7.32	< 0.001
Week 9	142.82	+/- 19.77	36.33	+/- 46.94	10.20	< 0.001
Week 11	148.71	+/- 20.17	27.50	+/- 42.24	12.38	< 0.001
Week 13	154.13	+/- 14.85	25.82	+/- 44.26	12.66	< 0.001

Undetectable yolk sac before embryo visualization in the first trimester suggests an abnormal intrauterine pregnancy[9] and is associated with miscarriage along with cases of yolk sac dimensions > 9 mm. and < 3 mm., irregularity in shape and numerous calcifications[10]. The current study showed that the largest yolk sac diameter in abnormal cases was less than 3 mm., yolk sac diameters

differed significantly between normal and abnormal pregnancies (Table 2) and that all cases of absent yolk sac had absent cardiac activity. However, Rowling and co-workers[11], reported normal pregnancy outcomes in cases with non-visualized yolk sac at mean gestational sac diameter ranging between 8 and 19 mm. suggesting that a discrimination value of 20 mm. was associated with 100% specificity and positive predictive value.

Fetal cardiac activity represents the earliest proof of pregnancy viability, which can be documented at 36 days of gestation by transvaginal ultrasound[12]. Between 30 and 40% of implanted pregnancies miscarry in the first trimester mainly at a very early stage[13], however, this rate drops to between 2 and 5% once fetal heart is detected[14].

First trimester bradycardia, which is defined as a heart rate of more than 2 standard deviations below the mean rate for gestational age[15] can be a sign of abnormal cardiac development or arrest in the conductive system of the heart, which is mostly associated with chromosomal abnormalities and serve as a predictor for miscarriage[16]. A study done by[17] demonstrated that heart rates below 70 beats per minute and most heart rates below 90 beats per minute miscarry early in pregnancy, which agreed with the mean heart rate detected in abnormal pregnancies done in the current study (Table 2). The main cause of fetal bradycardia before 7 weeks gestation is chromosomal abnormalities[18].

Hamela-Olkowska[19], in a trial to establish first trimester reference ranges for fetal heart rate noticed that this is gestational age dependant with a steady increase up to 9 weeks, reaching the peak at 10 weeks then minimally declining by the end of the first trimester, however, the current study showed nearly a plateau towards the end of the first trimester (Table 3).

Table 3: Showing changes in embryonic heart rate in patient groups of all cases of the study during 5th, 6th, 7th, 9th, 11th and 13th week of gestation.

Gestational	Embryonic Heart rate		Difference		Paired t-test	Paired t-test
Gestational age in weeks	Range	Mean +/- SD	Mean	SD	t	P-value
Week 5	0.0 - 100.00	67.00 +/- 33.29				
Week 6	0.0 - 180.00	75.35 +/- 39.29	- 8.35	19.64	- 2.69	0.01
Week 7	0.0 - 162.00	96.05 +/- 47.87	- 29.05	24.85	-7.39	< 0.001
Week 9	0.0 - 180.00	110.88 +/- 57.74	- 43.88	35.53	- 7.81	< 0.001
Week 11	0.0 - 178.00	112.35 +/- 62.85	- 45.35	42.28	- 6.78	< 0.001
Week 13	0.00 – 173.00	112.62 +/- 66.73	- 48.47	43.55	- 6.49	< 0.001

The current study showed a significantly higher maternal age in the abnormal pregnancy group as compared to the normal group, which could be explained by the increased risk of chromosomally abnormal embryos as maternal age advances. The current study also showed a significantly lower hemoglobin level in the abnormal group, a possible explanation for this is that most cases who tend to miscarry tend to bleed for a period of time presenting as threatened miscarriage before actual miscarriage occurs.

As regards the relationship between pregnancy outcome and the number of previous miscarriages (Table 4) it was more or less evenly distributed in the group with abnormal outcome in contrast to its distribution in the normal outcome group where most cases occurred in those with 3 previous miscarriages decreasing sharply to reach zero in cases with previous 7 or more miscarriages which is a sensible finding.

Table 4: Relation between outcome and number of miscarriages.

Number of Miscarriage	Outcome Normal	Outcome Abnormal	Outcome Total	Chi-	square
	(No. & %)	(No. & %)	(N0. &%)		
2	4 (3.57%)	0 (0.00%)	4 (2.50%)		
3	72 (64.29%)	4 (8.33%)	76 (47.50%)		
4	24 (21.43%)	8 (16.67%)	32 (20.00%)		
5	8 (7.14%)	12 (25.00%)	20 (12.50%)		
6	4 (3.57%)	4 (8.33%)	8 (5.00%)		
7	0	4 (8.33%)	4 (2.50%)		
8	0	12 (25%)	12 (7.50%)		
10	0	4 (8.33%)	4 (2.50%)		
Total	112 (100%)	48 (100%)	160 (100%)	22.534	0.002

Conclusion

Multiple ultrasound parameters with serial examinations are better than a single parameter or examination in predicting pregnancy outcome in cases with recurrent unexplained first trimester miscarriage.

Larger multi-center studies with larger number of patients and compare to normal control women without RM are needed to support these findings.

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