Correlation between the Level of Serum C-Reactive Protein and The Fetal Ultrasonic Prediction of Threatened Abortion

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Abstract: Background: Spontaneous miscarriage is the involuntary termination of pregnancy before 20 weeks of gestation or spontaneous expulsion of fetus below a fetal weight of 500 g. The definition varies in duration of gestational age according to the countries and available facilities. Spontaneous miscarriage accounts for about 15% of pregnancies. 1% of it is recurrent. Several studies have been established using ultrasound parameters and biochemical markers, aiming to predict the outcome of pregnancy. **Objective:** This study aimed to predict abortion using blood C reactive protein and some ultrasonographic measurements at the 7th week of gestation. **Methods:** This prospective study was conducted on two hundreds pregnant women on the 7th week of gestation, evaluating the relation between C- reactive protein serum level and fetal heart rate in prediction of spontaneous abortion in women presenting with live pregnancies complicated by vaginal bleeding at 5–12 weeks' gestation with or without abdominal pain at the period from May 2015 to May 2018. The 200 women will be included in this study have singleton pregnancy between 5th and 12th week of gestational age calculated on the basis of the last menstrual period and confirmed by ultrasound examination. **Results:** The current study found that the use of MSD, MSD-CRL ratio and FHR is significant in predicting pregnancy outcome and low abortion risk. **Conclusion:** This study found that the use of MSD, MSD-CRL ratio and FHR is significant in predicting pregnancy outcome**. But CRL is not significant.

Keywords: Serum C-Reactive Protein; Fetal Ultrasonic Prediction; Threatened Abortion

1. Introduction

Spontaneous miscarriage is defined as the involuntary termination of pregnancy before the 20th week of gestation (dated from the last menstrual period) or spontaneous expulsion of fetus below a fetal weight of 500 gm **(Speroff and Fritz, 2005).**

Spontaneous miscarriage affects 15-20% of pregnant women, primarily in the first trimester whilst most are sporadic and non-recurrent **(Clark et al., 2003).**

Threatened spontaneous abortion is the diagnosis of a live fetus of less than 24 weeks' gestation in the presence of a history of vaginal bleeding and a closed cervix **(Muttukrishna et al., 2011).**

A number of morphological ultrasound features have been described to evaluate the risk of complete spontaneous abortion after threatened spontaneous abortion. In particular, the mean or average gestational sac diameter, gestational sac volume, crown–rump length, and fetal heart rate (FHR) with variable results **(Odeh et al., 2012)** and, in up to 20% of women with a clinical suspicion of early pregnancy failure, the ultrasound findings are inconclusive **(Swer et al., 2012).**

The embryonic/fetal heart rate in threatened abortion was useful prognostic factor. We can easily demonstrate the embryonic heart activity during the 6th postmenstrual week, and consequently calculate the embryonic heart rate. It shows that from the 5th to 9th weeks of gestation there is a rapid increase in the mean fetal heart rate from 110 to 175 beat per minute, it then gradually decrease to around 160 to 170 beat per minute. Some biochemical markers such as beta human chorionic gonadotropin (β-hCG), progesterone (P), C reactive protein (CRP) and estradiol (E2), are reported to be very helpful in predicting the prognosis of pregnancy either used alone or in combination **(Odeh et al., 2012).**

C-reactive protein (CRP) is an acute-phase protein secreted by the liver in response to inflammation. It was named as a protein that binds to the C-polysaccharide of the pneumococcal cell wall, and it can now be measured with high-sensitivity assays **(Vashist et al., 2014).**

Increased CRP levels in normal pregnancy and a clear association between CRP and normal pregnancy, support the clinical application of this diagnostic tool in early pregnancy, especially in combination with serial beta-hCG measurements **(Cohen, 2014).**

Maternal CRP levels are raised as early as 4 weeks gestation and thus that the maternal inflammatory response is established during the

earliest phases of implantation. It is hypothesized that an abnormal response (either exaggerated or absent) could cause some cases of miscarriage **(Sacks, 2004).**

The systemic inflammatory response in early pregnancy failure and in threatened spontaneous abortion was investigated and these studies have shown that monocyte expression of TNFα and circulating levels of TNFα, IFNγ, IL-10, IL-6, and TNF-R1 which are induced by CRP **(Muangchant and Pope, 2013)** were lower in women with threatened spontaneous abortion who subsequently miscarried, compared with women with normal pregnancy outcome **(Calleja-Agius et al., 2012).**

The authors found that women whose serum CRP level was greater than the 75% percentile had a decreased odds ratio for pregnancy loss **(Boggess et al., 2005).**

The knowledge of the ultrasound appearance of normal early pregnancy development and a good understanding of its pitfalls are essential for the diagnosis and management of early pregnancy failure. No single ultrasound measurement of the different anatomical features in the first trimester has been shown to have high predictive value for determining early pregnancy outcome. Ultrasound parameters combined with maternal serum hormone levels, maternal age, obstetric history and occurrence of vaginal bleeding have all been combined in multivariate analyses, with mixed results **(Jauniaux et al., 2005).**

Aim of the work

The purpose of the this study is to evaluate the role of C- reactive protein (CRP) in the prediction and management of spontaneous abortion in women presenting with live pregnancies complicated by bleeding at 5–12 weeks' gestation with or without abdominal pain.

2. Patients and Methods
Study Design:

It is a prospective controlled study evaluating the relation between C- reactive protein serum level and fetal heart rate in prediction of spontaneous abortion in women presenting with live pregnancies complicated by vaginal bleeding at 5–12 weeks' gestation with or without abdominal pain.

Methodology

The 200 women will be included in this study have singleton pregnancy between 5th and 12th week of gestational age calculated on the basis of the last menstrual period and confirmed by ultrasound examination.

- Study entry and duration.

- Recruitment and initial assessment:

During the pre-selection visit exclusion and inclusion criteria will be applied.

Inclusion criteria:
-   All women will be 18 to 45 years of age.
-   Spontaneous living singleton intrauterine pregnancies.
-   Gestational age (5:12) weeks.
-   Occurrence of vaginal bleeding with or without abdominal pain in the current pregnancy or in previous one.

Exclusion criteria:
-   Multiple pregnancies.
-   Extra uterine pregnancies.
-   Hydatidiform moles.
-   A spontaneous pregnancy with medical history (i.e. recurrent spontaneous abortion, endocrinological disorders and infertility treatment).
-   Obstetric indication of termination of pregnancy.
-   Women having received hormonal treatment or progesterone supplements.
-   Pregnancies with a difference of more than 3 days between LMP and crown– rump length.

Outpatient instructions beside bed rest at home, and education about signs and symptoms of complete abortion.

Subjects included in the study will be randomized in 2 groups:
-   **Group (A):** The study group will be consisted of 100 healthy women presenting with threatened spontaneous abortion in a spontaneous pregnancy with no medical history (i.e. recurrent spontaneous abortion, endocrinological disorders and infertility treatment).

Threatened miscarriage involves vaginal bleeding with a viable fetus under 20 week's gestation and a cervix that remains closed **(Saraswat et al., 2010; Debra Betts et al., 2012).**

Bleeding usually begins first, and cramping abdominal pain follows a few hours to several days later. The pain of abortion may manifest as anterior rhythmic cramps, a persistent low backache associated with a feeling of pelvic pressure; or as midline suprapubic discomfort **(Cunningham et al., 2010).**
-   **Group (B):** The control group will be consisted of an equivalent number of women with an uncomplicated singleton spontaneous pregnancy referred for a reassurance scan because of a previous history of one pregnancy loss or pelvic pain and case-matched for gestational age calculated from their last menstrual period (LMP), maternal age, body mass index and smoking status.

All the cases in the study will be subjected to:-
-   Written informed consent before the study.
-   Complete history with special concern to previous medical and surgical treatment.
-   Complete general and abdominal examination.

- Vaginal U/S for Confirmation of the gestational age.

The measurements at the age of gestation includes:
- Mean gestational sac diameter.
- Crown- rump length.
- Embryonic heart rate.

10 cc of blood will be collected for C- reactive protin measurement using Enzyme- linked immunosorbent assay (ELISA).

All pregnancies will be followed up till the completion of the 20th week of pregnancy. The adverse outcome is 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.

Ultrasound examination

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

Gestational age will be determined from the onset of the last normal menstrual period and corroborated by measurement of GSD and CRL.

Ultrasound will be performed to measure the mean gestational sac diameter (MGSD), the crown rump length (CRL), and Fetal heart rate (FHR).

The mean gestational sac diameter will be measured by the sum of the length, width, and height of the gestational sac divided by 3.

The MGSD- CRL will be calculated as the difference between the mean sac diameter and the crown rump length.

Fetal heart rate (FHR) measurements will be obtained transvaginally using M mode sonography; the heart rate will calculated as beats per minute by the software of the ultrasound machine after measurement by electronic calipers of the distance between two heart waves on a frozen M- mode image.

Blood Sampling and assay of C-reactive protin:

10 cc of venous blood samples will be collected at the first visit for the measurement of serum C-reactive protein level. The samples will be centrifuged at 4,000 rpm for 10 minutes, and the serum will be separated and frozen at –70C for assay. The assay will be carried out using Enzyme-linked immunosorbent assay technique (ELISA) for measurement of serum progesterone.

The measured concentration of serum CRP will be correlated with pregnancy outcome (i.e., whether the pregnancy miscarried or not).

Statistical analysis

The data will be analyzed using the Stata® 12 data analysis and statistical software package (Stata Corp LP, College Station, TX). Because some distributions are skewed in the subgroups with an abnormal outcome, all the data are presented as medians and lower and upper quartiles or interquartile range. Differences in median hormonal levels and ultrasound measurements between the study and control groups, and between a subgroup of women with threatened spontaneous abortion resulting in a full spontaneous abortion and the corresponding controls, will be tested with the Mann–Whitney (Wilcoxon) W rank test at the 95% confidence interval. Results were considered statistically significant at $P < 0.05$.

3. Results

This prospective study was conducted on two hundreds pregnant women on the 7th week of gestation at the period from May 2015 to May 2018. The aim of this study was to predict of spontaneous abortion risk by U/S measurements and CRP level at 7th week.

Same group was between 4-16 with mean ± SD 9.3 ± 3.11. Statistical analysis of the results showed significance.

Table (1) showed that the range of maternal age in patients who completed their pregnancy in control group was 18-34 with mean ± SD was 26.51 ± 4.44 while the range of maternal age in aborted patient in the same group was 18-35 with mean ± SD was 26.71± 4.45. Statistical analysis showed no significant value as P-value > 0.05.

Table (2) showed that The range of maternal age in patients who completed their pregnancy in patient group was 19-35 with mean ± SD was 26.62 ± 4.43 while the range of maternal age in aborted patients in the same group was 18-34 with mean ± SD was 26.58 ± 4.46. Statistical analysis showed no significant value as P-value > 0.05.

Table (3) showed that the gestational age in patients who continue their pregnancy in control group ranged between 43-48 days with mean ± SD 45.80 ± 2.08 while the range of gestational age in patients who aborted in the same group was between 40-52 with mean ± SD 46.17±2.18. Statistical analysis of the results showed no significance.

Table (4) showed that the gestational age in patients who continue their pregnancy in patient group ranged between 42-51 days with mean ± SD 46.5 ± 2.17 while the range of gestational age in patients who aborted in the same group was between 43-52 with mean ± SD 47.5±2.21. Statistical analysis of the results showed no significance.

Table (5) showed that the MSD in patients who continue their pregnancy in patient group ranged between 13-28.6 days with mean ± SD 20.51 ± 4.90 while the range of gestational age in patients who aborted in the same group was between 8-20 with

mean ± SD 14.49±4.92. Statistical analysis of the results showed significance.

Table (6) showed that the MSD in control group who continue their pregnancy in patient group ranged between 15-27.6 mm with mean ± SD 20.51 ± 4.90 while the range of MSD in patients who aborted in the same group was between 10.8-20 mm with mean ± SD 15.49±4.92. Statistical analysis of the results showed significance.

Table (7) showed that the CRL in patients who continue their pregnancy in patient group ranged between 3.1-10 days with mean ± SD 6.4 ± 2.00 while the range of CRL in patients who aborted in the same group was between 3-8 with mean ± SD 7.3 ± 1.8. Statistical analysis of the results showed no significance.

Table (8) showed that the CRL in patients who continue their pregnancy in control group ranged between 3.2-10 days with mean ± SD 6.5 ± 2.00 while the range of CRL in patients who aborted in the same group was between 3-7.9 with mean ± SD 7.24 ± 1.8. Statistical analysis of the results showed no significance.

Table (9) showed that the MSD-CRL in patients who continue their pregnancy in control group ranged between 8-20 days with mean ± SD 13.3 ± 3.66 while the range of MSD-CRL in patients who aborted in the.

Table (10) showed that the MSD-CRL in patients who continue their pregnancy in patient group ranged between 9-21 days with mean ± SD 13.3 ± 3.66 while the range of MSD-CRL in patients who aborted in the same group was between 5-18 with mean ± SD 11.5 ± 3.09. Statistical analysis of the results showed significance.

Table (21) showed that the FHR in patients who continue their pregnancy in patient group ranged between 95-160 days with mean ± SD 128.03 ± 20.3 while the range of FHR in patients who aborted in the same group was between 58-120 with mean ± SD 60.26 ± 19.42. Statistical analysis of the results showed significance.

Table (32) showed that the FHR in patients who continue their pregnancy in patient group ranged between 94-164 days with mean ± SD 128.03 ± 21.36 while the range of FHR in patients who aborted in the same group was between 54-126 with mean ± SD 61.26 ± 18.66. Statistical analysis of the results showed significance.

Table (43) showed that the CRP in patients who continue their pregnancy in control group ranged between 5.78-7.63 days with mean ± SD 6.65 ± 0.58 while the range of CRP in patients who aborted in the same group was between 4.95-7.80 with mean ± SD 6.89 ± 0.64. Statistical analysis of the results showed significance.

Table (54) showed that the CRP in patients who continue their pregnancy in control group ranged between 5.88-8.03 days with mean ± SD 6.65 ± 0.58 while the range of CRP in patients who aborted in the same group was between 6.01-7.86 with mean ± SD 7.32 ± 0.52. Statistical analysis of the results showed significance.

Table (65) showed that statistically non-significant positive correlation between C reactive protein versus sonographic parameters P. value (<0.05).

Table (76) showed that cases with abortion had lower MSD, MSD-CRL, and FHR compared to non-aborted group with high statistically significant difference between both groups (aborted and non-aborted groups) P. Value (<0.001). While, as regard CRL and C reactive protein there is no significant difference between both groups P.value (>0.05).

Table (87) showed that cases with abortion had lower MSD, MSD-CRL, and FHR compared to non-aborted group with high statistically significant difference between both groups (aborted and non-aborted groups) P. value (<0.001). While, as regard CRL and C reactive protein there is no significant difference between both groups P.value (>0.05).

Table (98) showed that MSD, MSD-CRL, FHR were considered highly valid markers and better positive than negative with higher sensitivity compared to progesterone and CRL. The cut off level of MSD was <17mm with sensitivity 91% and specificity 72% and accuracy was 92%. The cut off level of CRL was < 6.5mm with sensitivity 71% and specificity 58% and accuracy was 62%. The cut off level of MSD_CRL was 9mm with sensitivity 96% and specificity 78% and accuracy was 95%. The cut off level of FHR was <121b/mm with sensitivity 90% and specificity 88% and accuracy was 91%. The cut off level of C reactive protein was 6.4 (μg/mL) with sensitivity 62% and specificity 63% and accuracy was 61%.

Table (10): Distributions of maternal age in control group.

Groups	Maternal age in control group					T-test	
	Range			Mean	±	SD	t	P-value
Ongoing pregnancy	18	-	33	26.51	±	4.44	0.318	0.751
Aborted	18	-	34	26.71	±	4.45		

Table (11): Distributions of maternal age in patients group.

Groups	Maternal age in patient group				T-test	
	Range		Mean	±	SD	T	P-value
Ongoing pregnancy	19 - 35		26.62	±	4.43	0.316	0.753
Aborted	20 - 34		26.58	±	4.46		

Table (12): Distribution of gestational age by days in control group.

Groups	Gestational age by days in control group				T-test	
	Range		Mean	±	SD	T	P-value
Ongoing pregnancy	43 - 48		45.00	±	2.08	6.538	<0.712
Aborted	40 - 52		46.00	±	2.18		

Table (13): Distribution of gestational age by days in patient group.

Groups	Gestational age by days in patient group				T-test	
	Range		Mean	±	SD	T	P-value
Ongoing pregnancy	42 - 51		46.5	±	2.17	**6.537**	<0.711
Aborted	43 - 52		47.5	±	2.21		

Table (14): Distribution of the patients group as regard ultrasound parameter (mean sac diameter MSD).

Groups	MSD in patients group				T-test	
	Range		Mean	±	SD	t	P-value
Ongoing pregnancy	13 - 28.6		20.51	±	4.90	0.029	0.977
Aborted	8 - 20		14.49	±	4.92		

Table (15): Distribution of the control group as regard ultrasound parameter (mean sac diameter MSD).

Groups	MSD in control group				T-test	
	Range		Mean	±	SD	t	P-value
Ongoing pregnancy	15 - 27.6		20.51	±	4.90	0.023	0.977
Aborted	10.8 - 20		15.49	±	4.92		

Table (16): Distribution of the patient group as regard ultrasound parameter (crown rump length CRL).

Groups	CRL in patient group				T-test	
	Range		Mean	±	SD	t	P-value
Ongoing pregnancy	3.1 - 10		6.4	±	2.00	1.356	0.178
Aborted	3 - 8		7.3	±	1.8		

Table (17): Distribution of the control group as regard ultrasound parameter (crown rump length CRL).

Groups	CRL in control group				T-test	
	Range		Mean	±	SD	t	P-value
Ongoing pregnancy	3.2 - 10		6.5	±	2.00	1.356	0.177
Aborted	3 - 7.9		7.24	±	1.8		

Table (18): Distribution of the control group as regard ultrasound parameter (MSD- CRL).

Groups	MSD-CRL in control group				T-test	
	Range		Mean	±	SD	T	P-value
Ongoing pregnancy	8 - 20		13.3	±	3.66	3.481	0.001
Aborted	4 - 16		9.3	±	3.11		

Table (19): Distribution of the patient group as regard ultrasound parameter (MSD- CRL).

Groups	MSD-CRL in patient group				T-test	
	Range		Mean	±	SD	T	P-value
Ongoing pregnancy	9 - 21		13.3	±	3.66	3.483	0.001
Aborted	5 - 18		11.5	±	3.09		

Table (20): Distribution of the control group as regard ultrasound parameter (FHR).

Groups	FHR in control group				T-test	
	Range	Mean	±	SD	T	P-value
Ongoing pregnancy	95 - 160	128.03	±	20.3	2.044	0.042*
Aborted	58 - 120	60.26	±	19.42		

Table (21): Distribution of the patients group as regard ultrasound parameter (FHR).

Groups	FHR in patients group				T-test	
	Range	Mean	±	SD	t	P-value
On going	94 - 164	128.03	±	21.36	2.06	0.039*
Aborted	54 - 126	61.26	±	18.66		

Table (22): Distribution of the control group as regard (C reactive protein CRP).

Groups	CRP in control group				T-test	
	Range	Mean	±	SD	T	P-value
Ongoing pregnancy	5.78 - 7.63	6.65	±	0.58	2.706	0.007*
Aborted	4.95 - 7.80	6.89	±	0.64		

Table (23): Distribution of the patient group as regard (C reactive protein CRP).

Groups	CRP in patient group				T-test	
	Range	Mean	±	SD	T	P-value
Ongoing pregnancy	5.88 - 8.03	6.65	±	0.58	2.706	0.008*
Aborted	6.01 - 7.86	7.32	±	0.52		

Table (24): Correlation between CRP and other parameters

	CRP	
	r	P-value
Maternal age	-0.052	0.605
Gestational age by days	0.049	0.631
Parity	0.009	0.932
MSD	-0.051	0.613
CRL	0.181	0.071
MSD-CRL	0.012	0.909

Table (25): Comparison between the studied group (aborted, non-aborted groups) in control group as regard ultrasound measurements and C reactive protein (CRP).

		Outcome				T-test	
		Ongoing (n=86)		Aborted (n=14)		T	P-value
MSD	Range	13 - 28.6		8 - 20		4.176	<0.001*
	Mean±SD	20.5 ± 4.7		14.4 ± 3.7			
CRL	Range	3.2 - 10		3 - 7.9		1.356	0.177
	Mean±SD	6.5 ± 2.0		7.24 ± 1.8			
MSD-CRL	Range	9 - 21		5 - 18		3.481	<0.001*
	Mean±SD	13.3 ± 3.7		11.5 ± 3.00			
FHR	Range	95 - 160		58 - 120		3.279	<0.001*
	Mean±SD	128.03 ± 20.3		60.26 ± 19.4			
C reactive protein	Range	5.88 - 8.03		6.12 - 7.82		2.706	0.004
	Mean±SD	6.65 ± 0.53		7.43 ± 0.59			

Table (26): Comparison between the studied group (aborted, non-aborted groups) in patient group as regard ultrasound measurements and C reactive protein (CRP):

		Outcome					T-test	
		Ongoing (n=86)			Aborted (n=14)		T	P-value
MSD	Range	13	-	28.6	8	-	20	4.176	<0.001*
	Mean±SD	20.5	±	4.7	14.4	±	3.7		
CRL	Range	3.00	-	10	3	-	8.00	1.356	0.178
	Mean±SD	6.4	±	2.0	7.30	±	1.8		
MSD-CRL	Range	8	-	20	4	-	16	3.481	<0.001*
	Mean±SD	13.3	±	3.7	9.30	±	3.10		
FHR	Range	94	-	164	54	-	126	3.279	<0.001*
	Mean±SD	128.03	±	21.36	61.26	±	18.6		
C reactive protein	Range	5.78	-	7.63	4.95	-	7.80	2.706	0.007*
	Mean±SD	6.65	±	0.53	5.89	±	0.64		

Table (27):   Validity of different markers for prediction of abortion and non-abortion.

ROC curve between abortion and non-abortion						
Variables	Cut off	Sens.	Spec.	PPV	NPV	Accuracy
MSD	<17mm	91	72	78	90	92
CRL	<6.5mm	71	58	57	62	62
MSD-CRL	9mm	96	78	77	96	95
FHR	<121b/min	90	88	89	93	91
CRP	6.4 (µg/mL)	62	63	59	58	61

4. Discussion

This study aimed to predict abortion using blood C reactive protein and some ultrasonographic measurements at the 7th week of gestation.

The current study showed that average age of the control group was 26.51 years with a range from 18-34 years (table5), the mean gestational age in days was 46 with average from 40-52 days (table7), the parity has been ranged from 0-6 (Table 9).

While in patient group the average maternal age was 26.72 with a range from 19-35 (table 6), the mean gestational age in days was with average from 42-52 (table 8), the parity has been ranged from 0-5.

The present study showed that 45% of the studied cases in the control were PG, while those in patient group were 47%. Para 1 in control group were 29% while those in patient group were 29% and 12% were Para 2 in control group and 13% in patient group respectively (Table 9).

The outcome of the present study was 86% of the studied cases in control group continued their pregnancy, while 85% of the studied group in the patient group continued (Table 3).

In the current study there was high statistically significant difference between aborted and non-aborted patients in both group (control group, patient group) in parity that the aborted group had higher parity compared to the continued group and P. value (<0.001)

This was in agreement with the results of **Jauniaux et al. (2015)** who revealed that high parity is risk factor of miscarriage in the first trimester. And in the present study there was no statistically significant difference between both group in gestational age and maternal age, but in contrast **Jones and Jerman (2014)** reported that high maternal age (> 40 years old) is a risk factor for abortion due to aneuploidy pregnancies in older age and also **Jauniaux et al. (2015)** revealed that high maternal age is a risk factor of miscarriage. This may be due to young ages of the cases involved in our study (< 35 years old).

The present study showed that the mean of MSD in control group was17.8mm and ranged from 10.8 - 27.6mm, mean of CRL was 6.6 mm and ranged from 3-10mm, while the mean of MSD - CRL was 12.9mm and ranged from 4-20 and mean of FHR was 109 b/min and ranged from 95_160 b/min.

The present study showed that the mean of MSD in patient group was18.8mm and ranged from 8 – 28.6 mm, mean of CRL was 6.67 mm and ranged from 3-10 mm, while MSD - CRL was 13 mm and mean of FHR was 106 b/mn and ranged from 54-164 b/min.

The current study showed that the aborted patients had lower MSD, MSD_CRL, and FHR compared to non-aborted group with high statistically significant difference between both groups and P. value (<0.001). While as regard CRL there is no

significant difference between both groups and P. value (>0.05), This result was supported by **Pepys and Baltz (1993)** did a retrospective study in order to determine the effect of MGSD, CRL and FHR measurements on the prognosis of pregnancy. A total of 274 patients at 5-9 weeks of pregnancy who were examined by transvaginal sonography were evaluated. They reported that these measurements in the first trimester could be used to predict the prognosis of gestation. This report support the result of the current study in the use of MSD, and FHR in prediction of abortion, but CRL is not.

Similarly; **Varelas et al. (2008)** in a prospective cohort study of 219 women found that the FHR progressively increase in healthy pregnancies during the first trimester. Fetal bradycardia is a predictor of poor pregnancy outcome during the first 12 weeks of pregnancy. This supports the results of the current study for fetal heart rate.

Altay et al. (2009) they did a prospective study of 99 pregnant women at the 10th week of pregnancy with the use of MSD, CRL, and Fetal heart rate as a predictor of spontaneous abortion risk they found that MSD_CRL ratio could predict patients with low abortion risk. The current study found that MSD, MSD_CRL ratio and fetal heart rate are predictors of low abortion risk.

In contrast; **Reljic (2001)** reported that the measurement of fetal CRL might be a useful predictor of spontaneous miscarriage in pregnancies with threatened miscarriage. The current study did not find similar results for CRL. This difference may originate from the difference of the study samples, as the study did not include the patients with threatened abortion.

In this study, ROC curve constructed to evaluate the role of sonographic parameters and CRP level as predictors of pregnancy loss; it was found that the best cut off point for MSD is 17 mm with a sensitivity and specificity of 91% and 72% respectively. And the best cut off point for CRL is 6.5 mm with a sensitivity of 71% and specificity of 58%., PPV and NPV of 57% and 62% respectively. The best cut off point for MSD_CRL ratio is 9 with sensitivity and specificity of 96%, 78% respectively, PPV and NPV 77%, 96% respectively. The best cut off point for FHR is 121 b/m with a sensitivity and specificity of 90%, 88% respectively, PPV and NPV of 89%, 93% respectively. This study was supported by **Tadmor et al. (1994)** reported that the cut off point for MSD_ CRL <5 mm could predict abortion; in this study, it was found that a threshold level for MSD_CRL < 9 mm could predict abortion. They evaluated first trimester abortions in 603 women in a prospective study, to compare gestational sac size, CRL, and fetal heart rate in the prediction of abortion before 13 weeks of gestation. They reported that GSD-CRL

ratio had a higher sensitivity than fetal heart rate in predicting pregnancy outcome. This report agrees with our study in that sensitivity of GSD_CRL was 96%, while sensitivity of FHR was 90%. **Tadmor et al.,** also reported a threshold level for FHR as <85b/min to predict abortion.

Abdallah et al. (2011) could not define a lower limit for gestational sac growth that could predict pregnancy loss with 100% specificity. The same investigation also demonstrated that very slow fetal growth could be seen in some viable pregnancies, resulting in a necessity to lower the fetal growth cut-off value for non-viability to <2 mm/day to attain 100% specificity. This recommendation was not included in the RCOG criteria.

In the present study, mean serum C reactive protein in patients who aborted in control group was 7.43 ng/ml with a range from 6.12 – 7.82 ng/ml, while its mean in patient who continue their pregnancy in the same group was 6.65 with a range from 5.88 -8.03 in comparison between both groups as regard CRP the mean of CRP in patients who aborted in the patient group was 5.89 with range from 4.95 – 7.80 while the mean of CRP in patients who continue their pregnancy in the same group was 6.65 with range from 5.78 – 7.63.

In the present study as regard CRP level there was no statistically significant difference and P. value (>0.05).

Similarly; **Jauniaux et al. (2015)** in a prospective controlled study of using bio-chemical marker in the prediction of pregnancy outcome Maternal serum high-sensitivity C-reactive protein (HSCRP) was evaluated in predicting spontaneous abortion in spontaneous pregnancies presenting with threatened spontaneous abortion. Seventy-one cases of threatened spontaneous abortion (group A) and 71 asymptomatic controls (group B), matched for gestational and maternal age, body mass index and smoking status, were included. Maternal serum samples were evaluated for HCG, progesterone, pregnancy-associated plasma protein-A (PAPP-A) and HSCRP using standard bio-assays. No difference was observed in ultrasound measurements, and median progesterone maternal serum level was significantly lower (P < 0.05) in group A compared with group B. In group A, the median of all ultrasound and maternal serum parameters was significantly lower (P < 0.01) compared with group B. The median gestational sac diameter, volume and median HSCRP and PAPP-A levels were significantly increased (P < 0.05) in group A, with a normal outcome compared with group B, probably owing to the inflammatory reaction associated with intrauterine bleeding. In group A patients destined to abortion, the gestational sac development and corresponding protein synthesis fell

before the fetal heart activity stopped; in spontaneous pregnancies, maternal serum HSCRP did not provide additional information for the management of threatened spontaneous abortion but warrants further research

Also, **Belo et al. (2005)** in a longitudinal study clarified the changes in serum C-reactive protein (CRP) levels and in the neutrophil activation state during normal human pregnancy. Concerning CRP levels, no consistent changes were observed throughout gestation; 12 cases (52.2%) presented fluctuations, whereas 7 (30.4%) showed progressive reductions and 4 (17.4%) progressive increments throughout pregnancy.

Similarly, **Rekha et al. (2016)** established a systematic review and meta-analysis of prospective studies that investigated biochemical markers to determine outcomes for women with threatened miscarriage at 5–23 weeks gestational age**.** They found that in women with threatened miscarriage, serum CA 125 has high predictive value in identifying pregnancies that are 'likely to continue, whereas the most commonly used biomarkers of serum hCG, progesterone and CRP are not useful in predicting outcome of a pregnancy with a viable fetus. Other markers such as inhibin A and a combination of markers need to be investigated to hopefully improve the prediction of outcome in women with threatened miscarriage.

But there was some reports disagree with our study they reported that CRP is a predictor of spontaneous abortion, for example **Cohen (2014)** examined the association between CRP levels and abnormal first trimester pregnancies. The results support single CRP measurement as a diagnostic tool in early pregnancy.

Similarly; **Sacks et al. (2004)** found that Maternal C-reactive protein levels are raised at 4 weeks gestation healthy pregnancy. So it can be used as predictor for ongoing pregnancy.

Chai et al. (2012) and Johns and Jauniaux (2006) suggested that serum HSCRP and PAPP-A could be useful in the screening of those women who have become pregnant through assisted reproduction techniques at risk of premature delivery after first-trimester threatened spontaneous abortion.

Scholl et al. (2011) found that high hsCRP is a diet-related biomarker for serious complications and poor pregnancy outcome in lean women with normal glucose tolerance.

Bondarenko (2018) in retrospective analytical study for evaluation of serum hs-CRP during various periods of pregnancy in women infected with parvovirus B19 infection found an increased level of the marker of systemic inflammation hs-CRP in the blood serum testifies to its active participation in the launch of a complex mechanism for the development of labor activity and the occurrence of fetal disorders, which was confirmed in groups of pregnant women with clinical complications in different pregnancy periods.

Similarly, **Archana et al. (2011)** in a prospective cohort study carried out to evaluate the role of early second trimester high sensitivity C - reactive protein for prediction of adverse pregnancy outcomes. Total 150 early second trimester primigravidae were analyzed for serum hsCRP level which was measured by immunoturbidimetry assay and followed till delivery. A statistically significant correlation was found between elevated serum hs-CRP concentrations in early second trimester primigravidae and adverse pregnancy outcomes like preterm delivery and pregnancy induce hypertension (p<0.001). This study reveals that elevated serum hs-CRP concentration observed in early second trimester primigravida could help to predict adverse maternal and fetal outcomes and if timely preventive prophylactic therapies are tried, would help to prevent morbidity and mortality due to pregnancy disorders.

The current study found that the use of MSD, MSD-CRL ratio and FHR is significant in predicting pregnancy outcome this is which supported by the results of studies by **Burwinkel et al. (1993); Tadmor et al. (1994); Doubilet et al. (2000); Makrydimas et al. (2003); Daemen et al. (2007); Varelas et al. (2008); Metin Altay et al. (2009) and Fatma and colleagues (2011).** But CRL is not significant.

Also the current study found that the measurement of serum CRP alone for prediction of pregnancy outcome is non- significant which is supported by the results of the studies of **Jauniaux et al. (2015), Belo et al. (2005) and Rekha et al. (2016).**

On the other hand there is many studies support the use of serum CRP measurement in the prediction of the fate of pregnancy **Cohen (2014), Sacks et al. (2004), Chai et al. (2012); Johns and Jauniaux (2006) and Scholl et al. (2011).**

Conclusion

This study found that the use of MSD, MSD-CRL ratio and FHR is significant in predicting pregnancy outcome**.** But CRL is not significant.

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