Can Maternal Serum High Sensitivity C-Reactive Protein Predict Outcome of Threatened Miscarriage?

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ABSTRACT

Background: Subclinical systemic inflammation may impede maternal immune tolerance, and implantation and embryonic development might be compromised. Inflammation could also be a causative factor for a proportion of miscarriages. As inflammatory reactions have a role in the occurrence of miscarriage, threatened miscarriage may be associated with higher maternal serum levels of High Sensitive - C reactive protein (HS-CRP) than in average, uncomplicated pregnancy.

Objective: To assess the accuracy of maternal serum (hs-CRP) in predicting pregnancy outcomes in women presenting with threatened miscarriage.

Study Design: Observational prospective cohort study included 200 pregnant women seeking antenatal care subdivided into two equal groups; Study group: 100 women with threatened miscarriage (presented by bleeding in early pregnancy, and Control group: 100 women with an uneventful pregnancy. All 200 pregnant women were under close follow-up every two weeks for vaginal bleeding and ultrasound assessment. For the quantitative measurement, maternal serum hs-CRP levels were evaluated by the Enzyme-Linked Immunosorbent Assay (ELISA) Kit.

Results: The mean serum level of HS-CRP (mg/dl) was significantly elevated in the study group (threatened miscarriage group) (8.73±1.55) than in the other group (5.17±2.04) in the control group ($P<0.001$). Miscarriage occurred in a more significant proportion in the study group (threatened miscarriage group) (40%) than their counterparts (10%) ($P<0.001$).

Conclusion(s): Maternal serum HS-CRP's levels were significantly higher in threatened miscarriage women than in average, uncomplicated pregnant women. This investigation suggests that pregnancy loss and chronic inflammation occur in association, so the relation between inflammation and pregnancy outcomes needs further investigation.

Keywords: hs-CRP, first trimester, miscarriage, pregnancy outcome, threatened abortion.

INTRODUCTION

The incidence of threatened miscarriage is 14-20%, which makes it the most typical complication that affects early pregnancy. It is diagnosed by vaginal bleeding with a pregnancy of fewer than 24 weeks gestation, living fetus, and closed cervix uteri [1, 2]. Threatened miscarriage risks 10% to turn into complete miscarriage after six weeks of gestational age [3]. Furthermore, threatened miscarriage carries long-term unfavorable events, including preterm labor, fetal growth restriction, and abruptio placentae [4, 5].

While inflammation has a vital physiological role in ovulation and implantation [6,7], the maternal immune system must induce changes to tolerate embryonic semi-allograft and prevent pregnancy rejection. With the alteration of fetal-maternal tolerance, microinflammation causes implantation failure and miscarriage [8,9,10]. Thus, maternal inflammation dysregulation may be a risk factor for pregnancy outcomes [6,11,12,13,14]. The formation of sub-chorionic hematoma in threatened spontaneously may disturb placentation by forming a series of chronic inflammatory reactions and oxidative stress damage to the placenta; it also alters the synthesis of proteins, cytokines, and function of the trophoblast [1, 2,15].

Multiple studies evaluated the role of these proteins in the prediction of pregnancy outcome with variable results, rendered to small sample size, variable target populations, and different study methods used [16]. C-reactive protein (CRP) belongs to a family of pentraxin proteins; it is a ring-shaped pentameric protein found in plasma. Its concentrations rise due to inflammation, and it is secreted by hepatocytes [17]. Some studies reported high CRP concentrations associated with early pregnancy loss and preterm deliveries [10, 18].

High-sensitivity C-reactive protein (Hs-CRP) is commonly included in cardiovascular disease risk assessment and treatment [19, 20]. Recent researches declared that HSCRP can be applied in first-trimester screening for preeclampsia [21], in the prediction of long-term cardiac illness in pregnant women with hypertensive disorders [22], and in neonatal infections as a complication of chorioamnionitis [23].

The study aimed to evaluate the role of maternal serum High Sensitive - C reactive protein (hs-CRP) in predicting pregnancy outcomes in women presenting early pregnancy bleeding.

Patients and Methods:

Study Design:

An observational prospective cohort study to evaluate the liaison between maternal serum high sensitivity C reactive protein (hs-CRP) levels and pregnancy outcome in women diagnosed with threatened abortion.

Study population

Sample size: It included 200 pregnant women attending antenatal care clinics at the Department of Obstetrics and Gynecology, Al-Fayoum University Hospital, from March 2021 to March 2022.

Inclusion criteria:

All of these 200 women were singleton pregnant at a gestational age between (6+0) to (10+6) weeks and were in the age range of (20-40) years old with neither history of spontaneous miscarriage nor infertility. They all had no history of maternal medical disorders associated with pregnancy.

Exclusion criteria:

Women with 1-multifetal pregnancies, 2-extra-uterine pregnancies, and 3-hydatidiform moles, 4-Any history of spontaneous miscarriage and infertility, 5- and medical disorders associated with pregnancy (such as hypertension, diabetes mellitus, anemia, hematological disorders, endocrinological disorders, renal disorders, hepatic diseases, autoimmune diseases, and collagen vascular diseases), 6- In addition, women with fever and infectious diseases were excluded.

After enrollment, participants were divided into two equal groups; each group included 100 women:

1. Study group: included 100 women with threatened miscarriage. Threatened miscarriage was diagnosed by vaginal bleeding with or without abdominal pain, positive pregnancy test (urine and/or blood tests), ultrasound showing intrauterine gestational sac living fetus, and closed cervix uteri without passing the products of conception [24].
2. Control group: included 100 women with uncomplicated pregnancy.

The 200 women underwent first-trimester abdominal ultrasound examination by multi-operators using Voluson E6 GE Healthcare with a trans-abdominal transducer probe frequency of 7 MHz. to diagnose singleton intrauterine pregnancy and to assess fetal viability and gestational age. The gestational age was calculated from the LMP. Also,

ultrasound scan reported on the mean gestation sac diameter and the crown-rump length. They had routine laboratory investigations such as complete blood picture (CBC), coagulation profile (PT and PTT), blood glucose level, liver function tests (ALT, AST, Bilirubin), renal function tests (urea and creatinine), and urine analysis. Then highly sensitive CRP (HS-CRP) measurements were performed.

All the 200 Pregnant women were under close follow-up every two weeks at antenatal care clinics, where they all were assessed for any vaginal bleeding, examined by ultrasound, and HS-CRP maternal serum levels were evaluated for quantitative measurement. Pregnancy outcome was assured by phone calls. Thus, outcomes were reported as either a case of miscarriage or continued normal pregnancy.

The Enzyme-Linked Immunosorbent Assay estimated HS-CRP serum level (ELISA) Kit for the quantitative measurement of CRP in human serum (HS- CRP ELISA DSL-10-42100, Texas 77598-4217 USA, Omega Company. The concentration of HS-CRP below 3 mg / L was considered normal as a reference value.

Ethical Consideration: This research was approved by the Ethical Committee of the Faculty of Medicine, Fayoum University R (205). A written, fully detailed informed consent concerning tests was obtained from each patient.

Statistical methods: Data were coded and entered using the statistical package SPSS version 23. Data were summarized using mean and standard deviation for quantitative variables. When comparing two groups, comparisons were made using an unpaired t-test and variance analysis (ANOVA) with multiple comparisons and a post hoc test when comparing more than two groups. P-values less than 0.05 were considered statistically significant.

% change was calculated using the equation:

$$\frac{V1 - V2}{V2} \times 100$$

Where:

V1 = New value of study group.

V2 = Control value obtained from the control group.

Values are presented as mean ± SD. Results are rendered statistically significant if ($P < 0.05$).

RESULTS

Both groups were matched regarding participants' age, gestational age, and BMI. The mean age (years) of women in the study group was (32.17+/-5.44) and in the control group was (31.73+/-4.17) (P=0.522). The mean gestational age (weeks) was

(10.07+/-0.98) and (10.13+/-2.08) in the study group and control group, respectively (P=0.794). The mean BMI (kg/m2) was (30.93+/-4.8) and (31.75+/-3.53) in the study group and control group, respectively (P=0.170), as presented in table 1.

There was no significant difference in the mean values of gravity and parity versus the control group. The mean gravity in the study group was (2.27+/-0.16) and in the control group was (2.25+/-0.19) (P=0.422). The mean parity was (1.22+/-0.12) in the study group and (1.19+/-0.15) in the control group (P=0.120) in table 2.
As stated in table (3), ultrasound assessment of the crown-rump length (CRL) and the gestational sac diameter showed no significant difference in both groups. The mean CRL (mm) was (9.04+/-2.66) and (8.47+/-2.79) in the study group and control group, respectively (P=0.141). The mean sac diameter (mm) was (20.48+/-5.10) and (21.36+/-3.85) in the study group and control group, respectively (P=0.170).

Table (4) and figure (1) illustrate a highly significant increase in mean serum level of High sensitivity- C reactive Protein (HS-CRP) in the study group than in the control group. The mean serum level of HS-CRP (mg/dl) was (8.73+/-1.55) in the study group, while it was (5.17+/-22.04) in the control group (P<0.001), which made a statistically significant difference
between.

Pregnancy outcomes showed highly significant differences between both groups. The number of participants who had advanced gestation in the study group was significantly lower (60 women, 60%) than in the control group (90 women, 90%), making a highly significant difference (P<0.001). Miscarriage was significantly higher in the study group than in the control group. Miscarriage was reported in 40 women (40%) in the study group versus ten women (10%) in the control group (P<0.001), making a highly significant difference (Table 5 and figure 2).

DISCUSSION

Miscarriage is a harmful experience that causes deleterious physical and psychological trauma. Thus, women with a threatened miscarriage should receive the best available healthcare to maintain their viable pregnancy. Unfortunately, there is currently no specific test to predict miscarriage. However, many studies have been investigating miscarriage prediction [25]. Prediction of miscarriage may help limit pregnancy prolongation and limit unnecessary supplementation of progestin [26].

C-reactive protein (CRP) is elaborated by the liver. It combines to the c-polysaccharide of the pneumococcal cell wall and can be tested with high-sensitivity assaying methods [27]. CRP levels has multiple applications as in the diagnosis and follow up of various inflammatory and malignant situations [19]. It was used as a screening tool for preeclampsia [21] and, lately, showed a promising role in the screening of gestational diabetes in obese women [28]. Additionally, it is helpful in

the evaluation of the status of early placentation and the possibility of pregnancy failure [29].

In the current study, the demographic data, the mean values of maternal age, gestational age, parity, gravity, and BMI showed nonsignificant differences between both groups. These findings aligned with an earlier study that documented advanced maternal age as the most potent risk factor for miscarriage, with women over 42 years experiencing 50% miscarriage rates and women aged 45 associated with 75% rates [30]. In addition, the miscarriage rate increases with maternal age, obesity, and parity [31].

Desale et al., 2016 documented the vital role of inflammation in a successful pregnancy. They concluded that persistent inflammatory reactions and failure of resolution due to an imbalance of anti-inflammatory cytokine-producing cells carry the risk of adverse pregnancy outcomes [32]. In addition, *Kaplanoglu et al., 2015* stated the relation between inflammatory reactions and labor onset. They reported that uterine contractions, cervical effacement, and dilatation were associated with inflammation [33].

In our study, HS-CRP levels were significantly higher in the study group (threatened miscarriage group) than found in the control group. This agreed with *Jauniaux et al. (2015)*, who assessed HS-CRP levels in 71 participants with threatened spontaneous miscarriage versus 71 participants with an uneventful pregnancy. They reported significantly higher levels of HS-CRP in women with miscarriages than in ordinary women who continued pregnancy [5].
Jauniaux et al. (2015) and Burton et al., 2009 explained that Chronic intrauterine bleeding is associated with chronic oxidative stress within the gestational sac; that is explained by proinflammatory cytokines, anti-angiogenic factors, and trophoblastic aponecrotic debris secretion into maternal blood which explain the elevated serum level of HSCRP and PAPP-A in threatened spontaneous abortion [5,34].

Contrary to our study Boggess and his collages 2005 declared that women with serum CRP level higher than the 75% percentile had a decreased odds ratio for miscarriage [35]

Our research found no difference in sac diameter and CRL between both groups. Contradictory results were reported by *Jauniaux et al. l (2015)*, who stated that for women diagnosed with a threatened spontaneous abortion resulting in a term live birth, the median sac diameter and volume were significantly increased in the study group [5].
Threatened spontaneous abortion is also related to long-term obstetric complications related to placental membranes, such as premature rupture of the membranes and premature labor [3]. These complications are also caused by chronic oxidative stress, resulting in early pregnancy loss as we found that more than 40% of women (study group) with high maternal HS-CRP did not continue their pregnancy. However, we do not know the exact mechanism of early pregnancy serum CRP in resulting

miscarriage, PTB, and PPROM, but we can still control cases with high CRP levels for other risk factors of these consequences and eliminate them if possible.

In addition, a study by *Bondarenko (2018)* investigated serum levels of HS-CRP in 129 pregnant women infected with parvovirus B19 and 16 ordinary pregnant women and found a significantly increased level of HS-CRP in pregnant women infected with parvovirus B19 than in ordinary women. They reported that HS-CRP participates in the launch of labor activity and fetal disorders, which agrees with our research result [37].

However, as there are still some controversies about the role of inflammatory markers, such as CRP, in causing PTB or PPROM, further studies (with different sets of subjects and larger samples) are necessary before the association between CRP and PTB and PPROM can be established definitely and proper predictive values are obtained [38].

A possible limitation in the present study is that it was conducted in a small population, but as the subjects were a random sample of pregnant women in that city, their socio-economic factors were not much different.

Author's contribution: All authors have read and approved the final manuscript. Rehab Abdelhamid Aboshama: research idea, manuscript writing, and data collection. Kareem El-Nahhas: manuscript writing and data collection. M Zaatar: data collection and data analysis. Laila Ezzat Abdelfattah: study design manuscript writing and data collection.

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Table (1): Demographic data and clinical characteristics among the studied groups:

	Control group		Study group		P-Value	Significance
	Mean	SD	Mean	SD		
Maternal age (years)	31.73	4.17	32.17	5.44	0.522	NS
Gestational age (Weeks)	10.13	2.08	10.07	0.98	0.794	NS
BMI (kg/m2)	31.75	3.53	30.93	4.8	0.170	**NS**

Values are presented as mean ± SD, **NS**: Not significant.

Table (2): Gravity and parity among groups:

	Control group		Study group		P-Value	Significance
	Mean	**SD**	**Mean**	**SD**		
Gravity	2.25	0.19	2.27	0.16	0.422	NS
Parity	1.19	0.15	1.22	0.12	0.120	**NS**

Values are presented as mean ± SD, **NS**: Not significant.

Table (3): Ultrasound among groups:

	Control group		Study group		P-Value	Significance
	Mean	**SD**	**Mean**	**SD**		
crown-rump length (mm)	8.47	2.79	9.04	2.66	0.100	NS
Sac diameter (mm)	21.36	3.85	20.48	5.10	**0.170**	**NS**

Values are presented as mean ± SD, **NS**: Not significant.

Table (4): Serum High sensitivity- CRP level among groups:

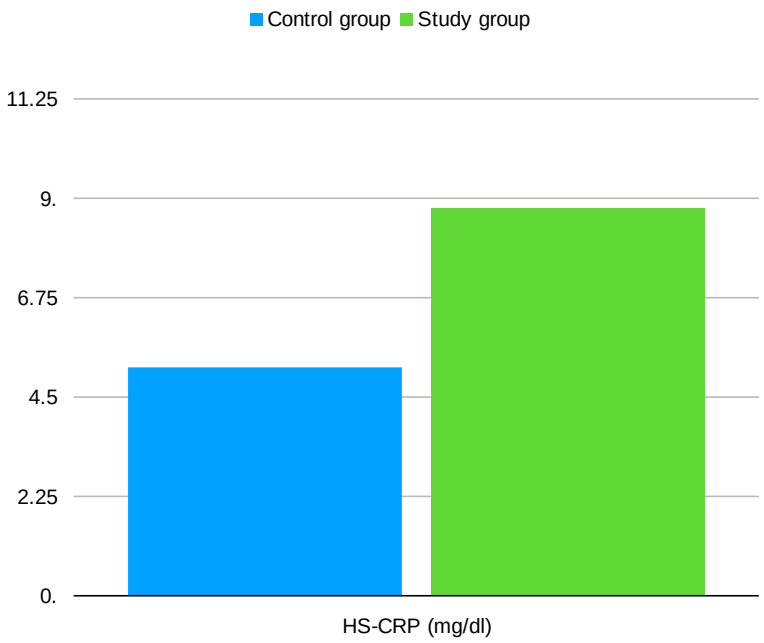
	Control group		Study group		P-Value	Significance
	Mean	**SD**	**Mean**	**SD**		
HS – CRP (mg/dl)	5.17	2.04	8.73	1.55	**< 0.001***	**HS**

Values are presented as mean ± SD, **HS**: Highly significant.

* Statistically significant compared to the corresponding value in the control group (P<0.001).

Figure (1): Serum High sensitivity- CRP level among groups.

* Statistically significant compared to the corresponding value in the control group (P < 0.001)



Pregnancy outcomes among the studied groups

Table (5): Pregnancy outcome among groups:

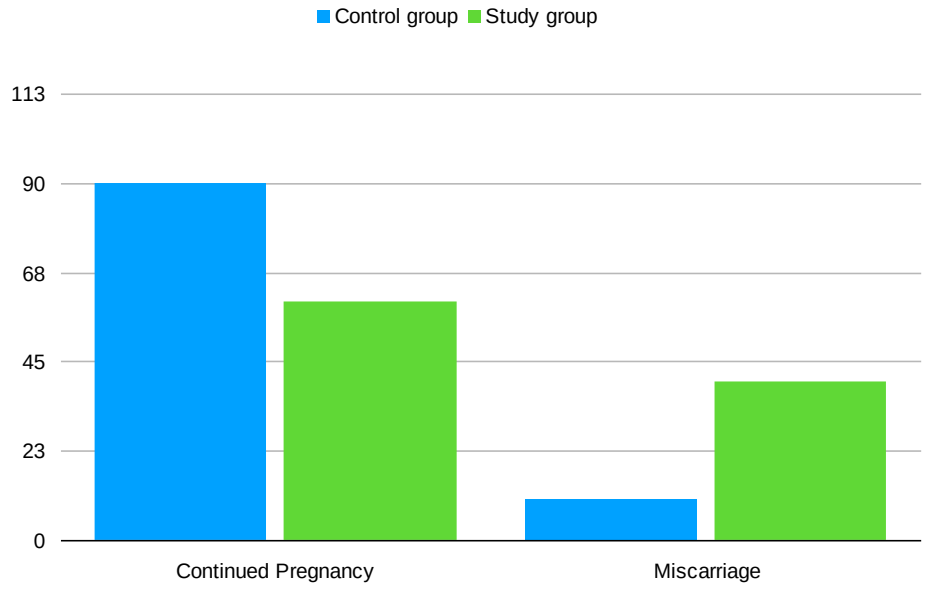
	Control group	Study group	P-value	Significance
Continue Pregnancy	90 (90.00%)	60 (60.00%)	< 0.001	HS
Miscarriage	10 (10.00%)	40 (40.00%)		

Values are presented as mean ± SD, **HS**: Highly significant.

* Statistically significant compared to the corresponding value in the control group (P<0.001).

Figure (2): Comparison of Pregnancy outcomes among groups.

* Statistically significant compared to the corresponding value in the standard group (P<0.001)



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