Troponin I, C-reactive protein and fibrinogen levels in missed abortions

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Summary

Objective: The aim of the study was to evaluate serum concentrations of troponin I, C-reactive protein (CRP), fibrinogen and ferritin levels in women with missed abortion and normal pregnancy. *Materials & Methods:* The study population consisted of 28 normal pregnancies and 28 pregnancies complicated by missed abortion. In all patients, troponin I, CRP and plasma levels of fibrinogen and ferritin were determined. *Results:* We found significantly elevated levels of CRP in the sera of the missed abortion group compared to the BMI-matched control group (4.3 ± 3.9 mg/l vs 2.4 ± 2.1 mg/l, $p = 0.035$). In addition, fibrinogen was decreased in the missed abortion group. No significant differences in troponin I and ferritin levels were detected between patients and controls. *Conclusion:* In this study we found an increase in CRP in women with missed abortion.

Key words: C-reactive protein; Missed abortion.

Introduction

"Missed abortion," which is defined as a nonviable pregnancy that has been retained in the uterus without spontaneous passage for at least eight weeks since the demise, implies that the uterus has "missed" recognizing the abnormal pregnancy. This term has its basis in the diagnosis of miscarriage before the development of ultrasound (US), where a discrepancy between the last menstrual period and uterine size by clinical examination was used to diagnoses a miscarriage [1, 2].

After the development of US, missed abortion in the first trimester has been characterized by an empty gestational sac or an embryo/fetus without cardiac activity which has not been expelled because the cervix is closed and unripe and no vaginal bleeding occurs [3]. Many other terms have been used to describe this event, including: silent or missed miscarriage, "anembryonic pregnancy", "blighted ovum", "early fetal demise", "nonviable pregnancy" and "embryonic/fetal death".

Inflammatory cytokines play an important role in the pathophysiology of recurrent miscarriage [4, 5]. Autoimmune factors have been reported to be frequently correlated with spontaneous abortion. Paradisi *et al*. revealed that particularly interleukin-10 might represent a useful diagnostic and prognostic marker for predicting the normal continuance of the pregnancy in threatened abortion [6]. In another study, women with threatened abortion had significantly lower serum levels of anti-inflammatory cytokine, but levels of proinflammatory cytokines were higher in this group compared with healthy controls [7].

While recurrent miscarriages [4, 5] and threatened abortions [6, 7] have been studied in a number of reports, missed abortions have been characterized to a lesser extent.

Our aim was to evaluate serum concentrations of troponin I, C-reactive protein (CRP), fibrinogen and ferritin levels in women with missed abortion and normal pregnancy.

Materials and Methods

We conducted a cross-sectional study over a one-year period. This study was approved by our Institutional Review Board, and all patients gave written informed consent. The study population consisted of 28 normal pregnancies and 28 pregnancies complicated by missed abortion. Subjects were eligible for enrollment if they were between 16 and 45 years of age. Gestational age was evaluated on the basis of the last menstrual period and confirmed by US.

Control group: A control group was composed of 28 healthy women with no history of previous miscarriage. All controls were singleton gravidas monitored at the Department of Obstetrics and Gynecology of our hospital with gestational age and body mass index (BMI) matched with the study group and no chronic medical disorders.

Missed abortion group: Patients with an embryonic disc developed with loss of viability most commonly demonstrating sonographically by an embryonic/fetal pole of ≥ 5 mm without gestational cardiac activity were accepted as the study group. Patients with severe uterine anomalies, thyroid dysfunction, glucose intolerance, kidney, or liver disease, pre-existing hypertension, history of thrombosis, or autoimmune diseases such as systemic lupus erythematosus were not included in the study. Patients selected for this study also had no known co-existing infectious diseases at the time of serum collection.

In all subjects, blood was drawn on admission in the morning after an eight-hour fast. In all patients, troponin I, CRP and plasma levels of fibrinogen and ferritin were determined. Nephelometric assay (Behring BN2, Germany) for CRP was performed using a commercial kit (Dade-Behring, N High Sensitivity CRP reagent kit). The assay has a detection limit of 0.1 mg/l. The day-to-day imprecision coefficient of variation

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(CV) at CRP concentrations of 0.16, 2.2 and 18 mg/l was 5.8%, 4.6% and 3.9%, respectively. Fibrinogen was measured using a clotting system (STA Compact Stago Diagnostica, France). The intra-assay and interassay coefficients of variation of fibrinogen assay used were, respectively, as follows: 1.44% to 3.85%, and 2.08% to 3.57%. Cardiac troponin-I concentrations were measured with commercially available ELISA-Kits. A clinically significant troponin I level was accepted as 2.3 ng/ml.

Statistical analysis of the data was performed with the software package SPSS for windows 11.0 (Statistical Package for Social Sciences; SPSS Inc. Chicago, IL). Kolmogorov-Smirnov analyses were used to test if the results were normally distributed. Comparisons between the two groups were performed using Student's *t*-tests or Mann-Whitney rank sum tests.

Results

Table 1 shows the clinical characteristics of the patients studied. No significant difference was observed in age between patients with normal pregnancy (control group) (mean SD, 26.2 ± 4.3) and those with missed abortion (study group) (27.3 ± 5.5). Gestational age and parity of the control group were similar to those of the study group.

We found significantly elevated levels of CRP in the sera of the missed abortion group compared to the BMI-matched control group (4.3 ± 3.9 mg/l vs 2.4 ± 2.1 mg/l, $p = 0.035$). In addition, fibrinogen was decreased in the missed abortion group. No significant differences in troponin I and ferritin levels were detected between patients and controls.

Table 1. — *Demographic and clinical characteristics of the two groups*.

	Missed abortion group	Control group (n = 28)	*p*
Age (years)*	27.3 ± 5.5	26.2 ± 4.3	0.492
Gravida**	3 (1-5)	2 (1-5)	0.065
Parity**	1 (0-3)	1 (0-2)	0.174
BMI (kg/m^2)*	24.7 ± 4.1	24.7 ± 4.6	0.961
Gestational age (days)*	56.6 ± 13.3	62.1 ± 17.1	0.202
Fibrinogen (mg/dl)*	341.2 ± 70.2	429.9 ± 73.9	0.0001
Troponin I (ng/ml)**	0.2 (0.2-0.41)	0.2 (0.2-0.24)	0.07
Ferritin*	23.6 ± 16.4	29.1 ± 17.7	0.325
CRP (mg/l)*	4.3 ± 3.9	2.4 ± 2.1	0.035

BMI: Body mass index; CRP: C-reactive protein. *Values are mean ± standard deviation. ** Values are median (minimum-maximum).

Discussion

Missed abortion consists of an intact fetal sac with or without a nonviable fetus which has not been expelled, because the cervix is tight and unripe and no vaginal bleeding occurs [3]. The causes of miscarriages remain unclear.

In a study by Hempstock *et al*., morphological and immunohistochemical markers of cellular stress and damage, including expression of heat shock protein 70, formation of N-Tyr residues, and lipid peroxidation were increased in tissues obtained from missed miscarriages compared with controls. The effect was greatest in those pregnancies of shorter than 77 days' duration and with evidence of recent fetal demise [8]. In another study, patients with missed abortion showed serum nitric oxide levels clearly decreased compared with nonpregnant patients and patients with regular pregnancy and threatened abortion [9].

In a study by Paradisi *et al*. soluble interleukin-2 receptor, in particular, IL-12, was detected with significantly higher levels in the missed abortion group compared with all other groups. With these results they supported a role of the immune system in the first trimester pregnancy and hypothesized that missed abortion may be associated with enhanced Th1 reactivity [10].

Missed abortion activates the release of inflammatory mediators leading to an inflammatory response. A systemic inflammatory response involves both the immune system and the clotting and fibrinolytic systems [11]. Fibrinogen is an important acute-phase reactant and is involved in a number of mechanisms (platelet aggregation, endothelial cell injury, plasma viscosity) that play a central role in the formation of thrombi. CRP is an acute-phase protein and nonspecific marker of systemic inflammation which is synthesized by the hepatocytes [12]. To the best of our knowledge, there are no data showing CRP measurement in missed abortions. In this study we found an increase in CRP in women with missed abortion. Elevation of CRP indicates enhanced inflammation and may help in identifying patients at high risk for adverse pregnancy outcome. Furthermore, we observed significantly decreased plasma fibrinogen levels in missed abortion, which may be caused by consumption. Troponin and ferritin levels did not show any significant differences between the two groups.

The physiological relevance of these findings and the mechanisms involved remain obscure. Further longitudinal studies are required to determine if increased levels of CRP can predict missed abortion.

CRP measurement may prove to be useful in clinical practice.

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