Quantitative measurement of the serum C reactive protein in different clinic categories of late spontaneous and therapeutic abortion

CARMEN A. BULUCEA¹, NIKOS E. MASTORAKIS², MARIANA F. PAUN¹, ALINA D. NEATU¹
¹Department of Obstetrics and Gynecology
University of Medicine and Pharmacy of Craiova
ROMANIA
²Military Institutes of University Education, Hellenic Naval Academy
GREECE

abulucea@gmail.com, mastorakis4567@gmail.com, aneatu@gmail.com

Abstract: - The goal of our prospective and controlled study was to dose the serum C reactive protein by Tina-quant immunoturbidimetric technique in parallel with leukocytes counting, in case of patients in the second gestational trimester with threatened abortion of unknown cause, that did or did not evolve towards spontaneous abortion during hospitalization, or with recurrent abortions in their priors, or with subclinical chorioamnionitis with or without broken membranes, or hospitalized for medical induction of the abortion for fetal reasons (such as retained dead fetus), or with acute pyelonephritis, subclinical mixed vaginitis or areolar mammary abscess, or with a normal pregnancy. Our results constantly indicate a significant (more accentuated after exogenous administration of prostaglandins in induced abortion) and maximum increase of serum CRP concentration (but not of the leukocytes number) at 24 hours postabortum, followed by a progressive decrease, of minimum 18%, of the same parameter, at 48 hours after non complicated second trimester abortion. Only the pregnancy complicated with high urogenital bacterial infections is accompanied by pathological values of the serum CRP (but not of the leukogram) that are significantly increased with respect to those from a normal pregnancy or one complicated with threatened abortion of unknown and non evolutive cause, or recurrent abortions in history. The obtained results suggest that a repeated measurement of the serum CRP concentration could be a valuable predictive marker for intrauterine infection, both in the late periabortum period as well as in the latency phase of the extremely premature rupture of the membranes or even when the fetal membranes are intact in the second trimester.

Key-Words: - CRP, intrauterine infection, second trimester pregnancy

1 Introduction

The second trimester spontaneous abortion, resembling the one occurring in the first trimester of pregnancy, knows six forms of clinic presentation, which can be synthesized as follows, according to Cristiaens & Stontenbeck [1], Rushton [2], Williams Obstetrics [3], [4], Hardaway [5], Delcroix & Gomez [6] and Munteanu [7]:

1. Threatened abortion is characterized by uterine bleeding in the first half of the pregnancy, to which, sometimes, a faint sacral or hypogastric pain can be associated.

It is assumed that uterine bleeding in late threatened abortion would originate either in the partial detachment of the placenta or in vascular anomalies from the place of implantation or union of the decidua capsularis with the decidua vera. The color of the uterine bleeding is initially a vivid red, but later changes to brown, corresponding to the end of the erythrocyte extravasation and coincident with the lysis of the clots surrounding the vessels involved in this gestational accident.

Unlike cervical lesions, that bleed especially after local traumas, or polyps exteriorized via the uterine cervical external orifice, or by the decidual reaction of the uterine cervix, in threatened abortion the clinical examination emphasizes only a uterus that is soft, pain free and of a size corresponding with the gestational age, whose cervix is closed, without pathologic lesions and only with the possible bleeding exteriorized via its external orifice.

Ultrasound examination is indicated to confirm the clinic diagnostic of threatened abortion. Ultrasound (real time) demonstration of fetal cord activity presence, possible transabdominally starting at 7 weeks of gestation, excludes the retention of a dead fetus as cause of uterine bleeding. In some case of threatened abortion, with a viable pregnancy, there can be echographically shown a second gestational sac, with no embryo,
The uterine bleeding in threatened abortion is often mild, but can last for days or weeks, which may not have immediate repercussions but can mean there is an increased risk of preterm labor, intrauterine growth restriction and perinatal morbidity.

The uterine bleeding in threatened abortion usually precedes, by hours or days, the possible abdominal pain, that can manifest as a cramp or can be continuous, intense, with a sacral, pelvic, diffuse or over the pubic symphysis location. Regardless of the character of the pain, the prognostic of pregnancy evolution in the presence of uterine bleeding associated with abdominal pain is reserved.

The traditional attitude towards threatened abortion was the physical and sexual rest. Considering the second trimester abortion etiology, it is obvious, excepting some cases of cervico-isthmic incompetence, that the bed rest is not justified, because it cannot influence the placental anomalies, the intrauterine infection or genetic anomalies. This is why, when the ultrasound demonstrated the viability of the pregnancy and the risk of threatened abortion evolving to abortion in progress is of only 2-3%, the mother must be morally supported, which, alongside sexual rest, is sufficient as therapy in the large majority of cases.

If the uterine bleeding in threatened abortion persists, the patient must be reexamined and the serum hemoglobin concentration and hematocrit retested. When the uterine bleeding is strong enough to cause anemia, as well as in case of dead fetus retention, it is mandatory to hospitalize the patient and evacuate the conception product, the pregnancy interruption being not only mandatory but also an emergency in case of abundant uterine bleeding, responsible for hypovolemia.

Therapeutic interruption of the second trimester pregnancy by means detailed in other papers published by the authors [8, 9, 10, 11, 12] must ensure a complete evacuation of the uterine cavity and the evacuated conception product must be systemically explored both macro and microscopically.

Moreover, threatened abortion in case of negative Rh pregnant women with positive Rh husband and absent anti-Rh antibodies in the peripheral blood imposes anti-D immunoprophylaxis, because in over 10% of such cases there were observed significant feto-maternal hemorrhages.

2. Abortion in progress (unavoidable) assumes macroscopic rupture of the fetal membranes associated to the uterine cervix dilation.

Rarely, in the first half of the pregnancy, there can appear a loss of amniotic fluid, without serious consequences. In such cases, the liquid might have been anteriorly collected, between the amnion and the chorion and escaped by rupture of the chorion, while the initial defect in the amnion is already healed.

If the sudden exteriorization of amniotic fluid, suggesting the rupture of the fetal membranes, precedes the abdominal pain or uterine bleeding, the patient must be supervised in bed rest conditions and hospitalization for possible repetition of the amniotic fluid debacle and/or installation of bleeding and uterine cramps or fever. In the eventuality that, after 48 hours of observation, no spontaneous amniotic fluid exteriorization happens, nor bleeding or uterine pain or fever, the abortion is considered unavoidable and the uterine cavity must be therapeutically evacuated.

The pain sensed by the patients with abortion in progress is due to the cervical dilation that seconds the uterine contractions, which in term, are explained, at least partially, by the release of prostaglandins, consecutive to the separation of the placenta and membranes from the uterine wall. With the opening of the internal orifice of the uterine cervix, the conception product will be incompletely expelled, in the vast majority of cases. Thus, the patient with abortion in progress can give information about the (partial) expulsion of the conception product. The uterine bleeding accompanying the inevitable spontaneous abortion can be considerable, fact that must not be underestimated.

In case of a physical examination of a patient with abortion in progress, it is observed a sensitive, rigid uterus that may be smaller than its gestational age, while the internal cervical orifice is opened, allowing direct palpation of the conception product.

Occasionally, the abortion in progress associates the shock, either secondary to the uterine hemorrhage which imposes adequate measures of volemic rebalance or disproportional with respect to the lost quantity of blood and due to the partial cervical retention of the conception product, with sympathetic stimulation (“cervical shock syndrome”). Removal of the conception product from the level of the uterine cervix is mandatory in order to efficiently fight the “cervical shock syndrome”.

3. Incomplete abortion. If the pregnancy is expelled intact, then the abortion is considered complete, but this is a rare spontaneous event, possible, usually, before 10
weeks of pregnancy; in most cases the conception product is partially spontaneously expelled, causing uterine bleeding and increased risk of infection in the absence of prompt treatment for complete evacuation of the uterine cavity.

In case of a physical examination, the incomplete abortion is characterized, alongside uterine bleeding, also by an open uterine orifice allowing direct palpation of fragments of intrauterine conception product that can sometimes coexist with other fragments of the same conception product but located in the vagina.

If the placenta, integrally or partially, is intrauterinely retained, the physiological hemostasis by efficient contraction of the myometrium is hindered and as a consequence, the placental bet vessels bleed diffusely, and, not rarely, abundantly, in the second trimester of pregnancy complicated with incomplete abortion, thus the increased risk of profound hypovolemia (rarely fatal) associated to this type of late abortion.

Most often, the late incomplete abortion does not necessitate cervical dilation before the complete and prompt evacuation of the uterine cavity by means of curettage, preferably a suction one, under local or general anesthesia and also in hospitalization conditions. The fever does not contraindicate the curettage if it is executed under adequate antibiotics treatment.

4. Dead fetus retention in second gestational trimester is defined as retention in the uterus, in the middle trimester of the pregnancy, of the conception product that has been dead for several weeks.

The patient with such a complication usually reports the disappearance of the pregnancy symptoms and signs (nausea, vomiting, mammary tension, increase in weight and abdomen dimensions, etc.) associated sometimes with the existence of a brown vaginal secretion, which may be the result of a progressive accumulation of unviable placentary tissue.

In case of a physical examination the uterus presents dimensions inferior to the gestational age, and the uterine cervical orifice is closed. Real time pregnancy ultrasound would confirm the retention of the dead fetus excluding the possibility of a viable pregnancy but with an inferior gestational age.

Sometimes the dead fetus retention, especially if it is prolonged and the fetus succumbed after the pregnancy entered the second gestational trimester, associates an increased risk of severe coagulation disorders manifested, for instance, by epistaxis or annoying gingival bleeding or in other minimally traumatized areas.

The reason why some abortions do not spontaneously end at an interval of several weeks after the death of the fetus is not clear. To this extent, threatened abortion therapy with prostogene is nowadays more and more suspected to contribute to dead fetus retention, being clearly demonstrated the fact that prostogene agents do not improve the threatened abortion prognostic but only delay the unavoidable.

For the case of dead fetus retention is also imposed therapy by evacuation of the uterine cavity, preceded by the preparation of the cervix with prostaglandins, as an example (as detailed in other of our papers [13, 14, 15, 16, 10, 11, 12]), to avoid the risk of cervical incompetence in subsequent pregnancies.

5. Spontaneous recurrent abortion is mentioned in the presence of at least three consecutive spontaneous abortions in priors.

Repetition of spontaneous abortions, in most cases, is a random phenomenon, since it has been observed that by using in these cases a large variety of alleged therapeutic methods that have nothing in common one with the other a prognostic favorable to the pregnancy was recorded in 70-90% of cases.

In late spontaneous recurrent abortions, the fetal development is most probably euploidal, while the maternal abortive anomalies are the most frequent cause.

Numerous morphopathological observations of the conception product systematically detect, in different proportions, both in late abortion as well as in preterm labor (that overlap in the period of 20 to 28 weeks of gestation [23, 6]), the placental ischemia and/or the acute amniochorioedidual inflammation as the most frequently involved pathological processes in the multifactorial and little understood etiology of the preterm labor [24, 25, 26, 27, 28, 29, 30, 31, 10, 32, 33, 34, 35].

It is estimated that uterine anatomic defects would contribute with up to 10% in the recurrent abortion etiology, although the exact value is not known; this is why when a woman with recurrent abortion is evaluated and it is discovered a uterine malformation either acquired or congenital, it is important to establish if there is a causal relation with her reproductive background [17].

Differentiating between the two main categories of spontaneous abortion causes (spontaneous abortions produced by zygotic anomalies and those provoked by maternal factors) assumes the compulsoriness of realizing, in principle, the karyotype (with banding) of the parents after three consecutive spontaneous abortions.

With the exceptions of the cases when there was observed via examination either the presence of antiphospholipid antibodies or an incompetent cervix, the chance of a pregnancy not complicated by abortion, after three consecutive spontaneous abortions, is of 70-85%, irrespective of the applied therapy, knowing nonetheless that the abortion risk increases from 30 to 45% if the three consecutive spontaneous abortions had not been preceded by a birth with alive fetus. On another
hand, today it is known that any woman with at least three spontaneous abortions in priors presents an increased risk such that the next pregnancy is complicated with preterm labor, placenta praevia, pelvic presentation and fetal malformations.

6. The septic abortion in the second gestational trimester presents itself under two main forms: either as an infection localized in the uterus or uterine annexes or as septic shock.

Septic abortion is usually caused by pathogen germs from the intestinal and vaginal flora and clinically presents, most often, as metritis, without implying that parametritis, peritonitis (localized and generalized) or sepsis are rare.

The septic abortion treatment includes the prompt and integral evacuation of the conception product. If the patient with septic abortion does not present severe uterine bleeding, as most often is the case, broad spectrum, systemic and large dose antibiotic therapy (proportional to the severity of the infection) must precede by 24 hours the uterine cavity evacuation, because the curettage exposes the arterioles to bacterial invasion. Moreover, the uterine curettage in case of septic abortion must be performed with utmost care, since the risk of Asherman’s syndrome is maximal for this kind of patients.

Serious complications like sepsis (up to septic shock), severe hemorrhages and acute renal insufficiency are much more frequently associated to the medically, and especially criminally, induced abortion, rather than to spontaneous abortion.

Persistent acute renal insufficiency (by renal cortical necrosis or renal tubular necrosis) complicating the abortion (not rarely from the second gestational trimester) is usually the result of the multiple effects (such as coagulopathy) of infection and prolonged acute hypovolemia, and rarely the consequence of the toxic effects of the “shock toxin” or some abortive agents (used with criminal purpose, such as soap), and prevention of this life threatening complication of the abortion imposes, among other things, careful handling of the fluid balance.

While the severe forms of septic shock frequently associates intense renal lesions, the lighter forms of the same type of shock rarely induce clinically manifested renal insufficiency.

Acute renal insufficiency is more severe when the cause of sepsis includes Clostridium perfringens, responsible for the production of a strong hemolytic endotoxin, and in such cases the precocious initiation of efficient dialysis proves to be welcomed, in order to prevent severe metabolic deterioration.

Spontaneous abortion (including the second trimester gestational one) is a very frequent pregnancy complication, but which receives little attention with respect to the associated risks, making the mortality rate due to abortion to reach 12.5 to a million pregnancies even in developed countries, the direct responsible factors for death in these cases being, in the first place, sepsis and/or hemorrhage associated to abortion.

All types of abortion associate uterine hemorrhage, whose magnitude is often impossible to quantify only via anamnesis, thus imposing a careful physical examination to the signs of acute anemia and implicitly the care for evaluating the sanguine group and sanguine compatibility, in order to apply a possible blood transfusion.

On another hand, the coagulopathy rarely complicates the late spontaneous abortion and this happens especially in cases complicated by sepsis or when the second gestational trimester dead fetus is retained in uterus more than a month. Although rare, the consumption coagulopathy is a severe complication that once discovered, it imposes a rapid and efficient therapeutic attitude, in collaboration with the hematologist and especially based on the administration of integral fresh blood and freshly iced plasma in the framework of a correct restoration of the volemia associated to antibiotic therapy and integral evacuation of the conception product from the uterine cavity.

Among the late complications of the second trimester spontaneous abortion, partially already enumerated, a special place is occupied by the severe psychic sequelae, necessitating a sustained and well conducted psychotherapy, of utmost importance for the success of the future pregnancy.

The C reactive protein stimulates the non-specific defense mechanisms of the body, its serum concentration increases 6 hours after the aggression (infectious, tissular lesion), reaching its peak after 1 to 3 days from the infectious/mechanic trauma and decreasing in 3 days from the attenuation of the inflammatory reaction that defines much more sensible than fever, leukocytosis and erythrocyte sedimentation rate (ESR) [36].

Serum C-reactive protein (CRP) dosing is, in its most recent version, the Tina-quant immunoturbidimetric method, as quick and cheap as counting leucocytes, but without the latter’s subjectivism and error factors and moreover without the risks of other, more invasive, evaluations of the infection that imply amniocentesis [37, 38, 10, 39, 40, 41].

It was demonstrated, on one hand, that after birth at term, either vaginal or abdominal, the serum CRP level increases significantly after 24 and respectively 48 hours, gradually decreasing in the uncomplicated postpartum [42], and on the other hand, between 27 and 37 gestational weeks, the pathological values of serum CRP significantly correlate with levels > 1500pg/ml of interleukin 6 from the amniotic liquid [43], while values of CRP < 2mg/dl indicate the absence of...
chorioamnionitis for the following 25 hours in 98% of preterm ruptured membranes [44].

2 Material and method
After obtaining the consent for supplementing the routine tests with serum C reactive protein dosing in parallel with counting leucocytes, the serum C reactive protein was quantitatively measured by the Tina-quant immunoturbidimetric technique on non-smoking pregnant women, in the second gestational trimester.

The selected patients were split in the following categories, prior to dosing the serum C reactive protein: a) 18 patients with normal pregnancies in the second trimester, identified with the occasion of prenatal consultations and whose results on the dosing from the peripheral blood served as control for the complicated pregnancies group; b) 10 patients, hospitalized for medical induction, with intravaginal prostaglandins, of abortion in the second trimester, for fetal reasons, such as: retained dead fetus, plurimalformed fetus, broken membranes in the conditions of a long cervix without uterine contractions or Rh isoimmunisation; c) 7 pregnant women with threatened abortion of unknown cause in the second trimester that evolved after 72 hours from the hospitalization with the spontaneous expulsion of the conception product.

In case of the patients from categories b) and c) the CRP dosing and the leukogram were performed both on admission as well as after 12, 24, 36 and 48 hours uncomplicated postabortion (the release at 72 hours post-abortum not identifying a pathology connected to the abortion, reconfirmed ambulatory after the first menstruation).

d) 12 pregnant women in the second trimester, for fetal reasons, such as: retained dead fetus, plurimalformed fetus, broken membranes in the conditions of a long cervix without uterine contractions or Rh isoimmunisation; e) 10 pregnant women in the second trimester hospitalized for investigations because of prior history of at least three consecutive spontaneous abortions (recurrent abortions, according to St. Mary’s NHS Trust criteria [17]);

f) 2 patients with extremely preterm broken membranes and extremely preterm (at 17 and respectively 19 gestational weeks) of approximately 24 hours and complicated with subclinical chorioamnionitis, confirmed via positive cultures for Escherichia coli, taken in a sterile manner with a transvaginal speculum; g) 6 patients with subclinical chorioamnionitis with intact membranes, in whose case taking blood for CRP and leukogram was performed once the presumption diagnosis was established (in the presence of two risk factors for chorioamnionitis such as a dead fetus and oligohydramnios, observable with an ultrasound). This presumptive diagnostic was sustained after taking blood for CRP by detecting the appearance of progressive uterine contractions, that culminated with the expulsion of the non-macerated fetus at approximately 48 hours from hospitalization and confirmed by the positive culture for E. coli or Staphylococcus coagulase-negative from the amniotic liquid taken sterile with a transvaginal speculum, immediately after the spontaneous rupture of the membranes during the abortion;

h) 5 patients with of acute pyelonephritis and 5 patients with mixed subclinical vaginitis (trichomoniasis and candidosis) associated in 4 cases with acute cystitis and in one case with areolar mammary abscess, incised after taking blood for CRP.

It is worth mentioning that the patients from the f), g), and h) categories had their temperature daily monitored, did not have painful uterine contractions and were not under antibiotic therapy for more than 48 hours at the time the venous blood for CRP and leukogram was taken.

The sensitivity of the Tina-quant serum CRP dosing test is 0,01mg/dl, while the upper limit of the normal case during pregnancy was 2mg/dl.

A value of p<0,05 represented a statistical signification when comparing results by means of the Student’s t and Mann Whitney U tests and respectively the analysis of the linear regression, as it was needed, mean values or correlations [45].

3 Results and discussions
The results of our study are depicted in tables 1 and 2.

As in case of the non-complicated postpartum [42] our results (table 1) constantly indicate a significant (more accentuated after exogenous administration of prostaglandins in induced abortion) and maximum increase of serum CRP concentration (but not of the leukocytes number) at 24 hours postabortion, followed by a progressive decrease, of minimum 18%, of the same parameter, at 48 hours after non complicated second trimester abortion.

Recognizing the constancy of such an evolution curve of the late non complicated postabortum serum CRP level presents a diagnostic significance for the complicated cases, for instance infectious.

Stimulating the serum CRP increase by exogenous administration of prostaglandins explains, at least partially, the significant growth of CRP postabortion and concords with prior observations on this relation, both postpartum [42] as well as outside of the pregnancy [46, 47].
### Table 1. Demographic characteristics, CRP and no of serum leukocytes/ml of the studied groups pre and post late abortum without complications

<table>
<thead>
<tr>
<th>Group</th>
<th>A. Second trimester pregnancy with fetal complications that impose medical induction of abortion (with intravaginal prostaglandins)</th>
<th>B. Second trimester pregnancy complicated with threatened abortion that evolved after 72 hours from check-in with the spontaneous expulsion of the conception product</th>
<th>A+B. 13-27 weeks pregnancies with non complicated postabortum evolution, spontaneous or induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Age</td>
<td>23.7±1.7</td>
<td>26.57±3.53</td>
<td>24.88±1.73</td>
</tr>
<tr>
<td>Parity</td>
<td>1.3±0.66</td>
<td>1.74±0.69</td>
<td>1.47±0.49</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>21.5±1.33</td>
<td>22.8±1.67</td>
<td>22.0±1.02</td>
</tr>
<tr>
<td>CRP mg/dl</td>
<td>Preabortum</td>
<td>1.35±0.36</td>
<td>0.72±0.06</td>
</tr>
<tr>
<td>[no leukocytes/ml] 24 (12 hours postabortum]</td>
<td>*3.31±0.55</td>
<td>*2.42±0.63</td>
<td>*3.22±0.38</td>
</tr>
<tr>
<td>48 (36 hours postabortum]</td>
<td>2.7±0.52</td>
<td>1.55±0.95</td>
<td>2.42±0.46</td>
</tr>
</tbody>
</table>

Table 2. Demographic characteristics, CRP and no of leukocytes/ml of the second trimester of normal and complicated pregnancy studied groups

Table 2 shows that only the pregnancy complicated with urogenital bacterial infections is accompanied by pathological values of the serum CRP (but not of the leukogram) that are significantly increased with respect to those from a normal pregnancy or one complicated with threatened abortion of unknown and non evolutive cause, or recurrent abortions in history.

### 4 Conclusions

1. The obtained results suggest that the dynamic measurement of the serum CRP concentration could prove to be a valuable and practical predictive marker of intrauterine infection, both in the late periabortum period as well as in the latency phase of the extremely premature rupture of the membranes or even when the fetal membranes are intact in the second trimester.

2. In this latter situation (intact fetal membranes in the second gestational trimester), given the observation in our study of the correlation between serum CRP and positive culture of the amniotic fluid, the less invasive serum CRP test could become a valuable screening for intrauterine infection on intact membranes in the middle trimester.

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