Correlations between clinic categories of late spontaneous and therapeutic abortion and C-reactive protein

Carmen A. Bulucea, Nikos E. Mastorakis, Mariana F. Paun, and Alina D. Neatu

***Abstract*—**In the first part of the paper there are synthesized the six forms of clinic presentation of the spontaneous abortion: threatened abortion, abortion in progress, incomplete abortion, dead fetus retention, spontaneous recurrent abortion and septic abortion, with an emphasis on late spontaneous recurrent abortion. In the second part there are presented the results obtained by the quantitative measurement of the serum C-reactive protein with the Tina-quant immunoturbidimetric technique on pregnant women in the second trimester of normal pregnancy, with threatened abortion of unknown cause, that evolved or not towards spontaneous abortion during the hospitalization, with recurrent abortions in priors, with subclinical chorioamnionitis with broken or intact membranes, with acute pyelonephritis, subclinical mixt vaginitis or mammary abscess or hospitalized for medical abortion induction for fetal reasons (for instance dead fetus retention). The obtained results suggest that a repeated measurement of the serum CRP could be a valuable and practical 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 of pregnancy.

***Keywords*—**CRP, intrauterine infection, second trimester pregnancy.

I. 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.

The local, very careful, clinic examination is important also for exclusion of the ongoing abortion, case in which the uterine cervix is already dilated, and the fetal membranes with continuity solution macroscopically evident, allowing exteriorization of amniotic fluid, as well as of ectopic pregnancy or torsion of an ovarian cyst not suspected before the complications.

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, indication of an unviable twin pregnancy. In such cases, repeating the ultrasound, one can observe the resorption of the unviable pregnancy sac, while the viable pregnancy evolves, most often, unaffected. The ultrasound may also exclude a low lying placenta, responsible for uterine bleeding at the end of the second trimester of pregnancy but also a hydatidiform mole.

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

C. A. Bulucea is with the University of Medicine and Pharmacy of Craiova, Obstetrics and Gynecology Department, Romania (e-mail: abulucea@gmail.com).

N. E. Mastorakis is with the Military Institutions of University Education - Hellenic Naval Academy, Greece (e-mail: mastorakis4567@gmail.com)

M. F. Paun, is with the University of Medicine and Pharmacy of Craiova, Obstetrics and Gynecology Department, Romania.

A. D. Neatu is with the University of Medicine and Pharmacy of Craiova, Obstetrics and Gynecology Department, Romania (e-mail: aneatu@gmail.com).

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 placentary 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 vacuity of the uterine cavity and the evacuated conception product must be systemically explored both macro and a 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 pregnant woman may be discharged, to resume all activities except sexual ones. If, nonetheless, the exteriorization of amniotic fluid is repeated and is accompanied or followed by bleeding and uterine pain and/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 expulsed, 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 expulsed 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 expulsed, 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 placentary 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.

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.

The genetic causes of an abortion correspond either to an observable alteration of the chromosomes (chromosomal aberrations, not transmissible in the majority of cases) or to a fine alteration of the DNA molecule, thus invisible, the genic anomaly, that is often transmissible and can be suspected based on statistic arguments, starting with the study of the genealogic tree, whose frequency in the abortion products is unknown [17].

The genetic abortion is classified as aneuploidal (characterized by chromosomal anomalies) and euploidal (when the conception products, chromosomally normal, are usually aborted in a more advanced stage of the pregnancy).

The karyotype anomalies are manifested in the conception product by particular modifications of the phenotype, synthesized by Vokaer [17]:

1. The X monosomias, that are frequent, represent 15% of the spontaneous abortion products. The embryos carrying an X monosomy present a stopped evolution, usually towards the eighth gestational week. Nonetheless, some overstep this critical period and constitute, together with the triploidias, the majority of observable aberrations in late abortions. During second trimester abortions, the X monosomy diagnostic is given very easy, due to the aspect of the fetus, which is always macerated and with anasarca, with cervical hygroma, quasi pathognomonic for the X monosomy, since it is present in all cases in which a cellular culture could be obtained.
2. The triploidias represent approximately 20% of the chromosomal aberrations observed in the spontaneous abortion products. The conception product carrying a triploidy possesses a very variable development potential, stretching from precocious abortion towards the fifth gestational week to a child born dead. After the tenth gestational week, the triploidy presents itself as a mole with embryo.

Ville and team [18] show that a chromosomal anomaly is often proven by a delay in the intrauterine growth, while Flori and collaborators [19] consider that, in case of a very young or on the contrary an old age of the mother, in case of a history of chromosomal anomalies, in case of ultrasound and biological alarm signs (the study of the maternal serum markers at 15-16 weeks of amenorrhea to discover the risk of trisomy 21) the prenatal cytogenetic diagnose is necessary.

It is important to underline the fact that the chromosomal errors appear sporadically and do not constitute, in the large majority of cases, a repeatable cause of spontaneous abortion [20].

A chromosomal anomaly of one of the parents is present in just 3-5% of the couples affected by recurrent abortion, most often being a mutual or Robertsonian translocation, and despite this small incidence of hereditary chromosomal anomalies, Wolf and Horger [21] demonstrate that including the parents and conception product karyotyping in the standard evaluation of the recurrent abortion would generate significant financial (1100 $ per investigated case) and emotional savings, as well as the correct attitude, for each investigated case.

In agreement with this last observation, the Rai group [22] synthesizes the conduct with respect to recurrent abortion by

chromosomal anomaly, like this: "Identification of the group, less numerous, of the couples with recurrent abortion of chromosomal cause is essential to ensure prompt application, to each of these cases, of specialized genetic counsel, presenting the couples the prognostic of future pregnancies, allowing also investigation and education of relatives, but also adequate prenatal exploration, in any future pregnancy".

If one compares the euploidal and the aneuploidal abortions, it can be noticed that ¾ of the aneuploidal ones appear before 8 weeks of pregnancy, while the euploidal abortions have a maximal incidence at approximately 13 weeks, but nonetheless happening also in the second trimester of pregnancy [23, 24].

Flint and Gibb [25] warned on the fact that the incidence of euploidal abortions increases dramatically after the age of 35 for the mother, but the causes of this phenomenon remain obscure, as the etiology of the euploidal abortions, for which, nonetheless, the following hypotheses are circulated: a) a genic anomaly, such as an isolated mutation or polygenic factors; b) various maternal factors (including smoking and alcohol excess); c) possible paternal factors.

The Williams obstetrics [3] shows that approximately 0.5% of children present chromosomal anomalies, while at least 2% of the alive newly born suffer of a disease associated with a unigenic mutation or with one inherited via a polygenic mechanism; these mutations can trigger abortion by alteration of various fetal functions or differentiation.

Fetal chromosomal anomalies (such as autosomal trisomias, especially D and G, in case of conception products of mothers of older age; the X monosomy, the only one associated with a young age of the mother; the triploidy; the tetraploidy; chromosomal structural anomalies and sex-chromosome polysomy [26, 3]) are numerically rare in case of women with recurrent abortions in priors (including late abortions); these women are not protected by a fetal disjunctional event so fetal karyotyping is important in all cases of recurrent abortion; nonetheless, detection of a fetal genetic anomaly for a woman in whose case the endocrine or autoimmune cause of the abortion is well established does not exclude application of a therapy adequate to the background anomaly in the respective case, with recurrent abortions in priors.

Classically, it has been assumed that many cases of spontaneous abortions, especially recurrent ones, sometimes manifested in the second gestational trimester (because, after the death of the fetus, the spontaneous expulsion of the conception product, in the absence of the ascending infection, often does not happen for several weeks [21]) are based on a background endocrinopathy.

Classical conceptions on associating diabetes mellitus and thyroid dysfunction with spontaneous (especially recurrent) abortion are no longer accepted since 1998 [20], because, on one hand, metabolically well controlled diabetes mellitus presents a risk of spontaneous abortion equal with that observed in the general population and only the ignored diabetes, indicated by increased levels of glycated hemoglobin is associated with an increased rate of spontaneous abortion, and, on the other hand, the alleged association between the increased risk of spontaneous abortion and the presence of thyroid autoantibodies is in fact the consequence of a generalized autoimmune disease, because thyroid function tests are usually normal in recurrent abortions. This is why, in practice, the thyroid function and tolerance to glucose tests are not applied anymore, as being non-informative [21].

Inadequate progesterone secretion by the ovary or placenta in the second half of the menstrual cycle and during pregnancy was considered for a long time as cause that would affect between 20 and 60% of women with recurrent abortion [22].

Because there was no efficient method to diagnose the luteal phase defect in pregnant women, the diagnostic was based on progesterone dosing and endometrial biopsies in the infertile cycles [3]. Moreover, the profiles of the ovarian steroid hormones, before implantation, in the fertile cycles are similar to those in a pregnancy evolving normally or complicated by an abortion [3]. That is why it is not surprising the conclusion that the progesterone substitution is useless when suspecting luteal phase defect, resulted from the meta-analysis of six multicentre studies, when the exogenous progesterone administered after conception did not prove any benefice [20].

Despite these convincing data, a lot of women keep receiving progesterone and shots of human chorionic gonadotropin during pregnancy, to no avail, knowing just that up to today there was not shown any fetal malformative risk of the progesterone therapy [3].

The modern conception about the endocrine background of the abortion (especially the recurrent one) is concentrated on the relation between spontaneous interruption of the pregnancy, in its first half, and the polycystic ovaries and hyper secretion of luteinizing hormone, starting from the observations of the assisted reproduction clinics (later confirmed also in the case of women with spontaneous conception, following regular cycles), indicating the elevated LH serum level (most often) as marker of subfertility and precocious abortion [20].

There are two mechanisms that try to explain the relationship between LH hyper secretion and decreased reproductive performance: 1) abnormally high LH level generate the premature resumption of the second meiotic division of the oocyte, conducting to the release of a physiologically aged egg; 2) LH, by direct effect on the endometrium would disadvantage the implantation [22].

Rai and team [22] were reporting ultrasound diagnose of polycystic ovaries in 58% of women with recurrent abortions, and in 56% of these cases, based on the matutinal LH urinary screening, hyper secretion of LH is identified, reason for which the same group started evaluating the effect of the pituitary desensitization therapy with analogues of gonadotropin releasing hormone on pregnancy, agent that inhibits the endogenous secretion of LH.

In 1998, St. Mary's NHS Trust [20] indicates, in case of

pregnant women with recurrent abortions in priors, in whose case the presence of polycystic ovaries and LH hyper secretion are identified, as being sufficient for the success of the pregnancy, strict surveillance of the pregnancy in the first trimester by clinic and ultrasound weekly examination, associated with psychotherapy and repetition, at least once, in the first weeks of gestation, of antiphospholipid antibodies dosing, because preliminary results on LH suppression therapy for this category of patients do not seem to bring any supplementary benefice.

Infectiously induced independent immune perturbations are frequently incriminated in the etiology of the recurrent abortion [3, 20, 27, 28, 29, 30, 31].

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 [32]), the placental ischemia and/or the acute amniochoriodecidual inflammation as the most frequently involved pathological processes in the multifactorial and little understood etiology of the preterm labor [33, 34, 35, 36, 37, 38, 39, 40, 10, 41, 42, 43, 44].

Vokaer [17] states that the mechanic causes of spontaneous abortions are essentially split in ovular causes: multiple pregnancies and hydramnios and uterine causes:

1) uterine cavity anomalies - uterine hypoplasia and hypotrophy, malformed uteri (unicornuate, bicornuate, uterus didelphys, uterine septum), myoma, uterine synechiae (only partial synechiae being compatible with a pregnancy);

2) cervico-isthmic incompetence.

In case of uterine hypoplasia and hypotrophy, to the reduced dimensions of the uterine cavity there is also associated a certain degree of malformation.

To the dimensions and shape anomalies sometimes there are also associated:

a) a modification of the muscle structure, characterized by the predominance of fibrous tissue with respect to the muscle tissue;

b) a possible modification of the direction and architecture of the myometrial fibers, also compromising the functional quality of these uteri;

c) a vascularization insufficiency that will explain the reduced thickness of the wall and the low quality of the mucosa;

d) a uterine cervical incompetence, that may become apparent only during pregnancy, as in the case of utero-placental insufficiency following lateral placentation associated to Mullerian duct anomalies [45].

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 (such as leiomyomata – important for the abortion more by localization rather than dimensions, or uterine synechiae, which would generate recurrent abortion by means of endometrium insufficiency of implantation) or congenital (forming abnormality or Mullerian ducts fusion, either spontaneous or induced by exposure to Dietilstilbestrol), it is important to establish if there is a causal relation with her reproductive background [20]. For instance, if a uterine septum is detected, a repeated implantation of the embryo on this septum is improbable, for the appearance of precocious recurrent abortion [22]. Moreover, the Rai group [22] discovers a similar incidence of uterine anomalies in case of 500 women with recurrent abortion, as well as among 680 parous women, with normal reproductive history, 3% Mullerian duct anomalies of which 90% septated uteri and 5% bicornuate uteri.

On the other hand, St. Mary's NHS Trust [20] shows that classic, transperitoneal surgical intervention for the uterine anomalies associate a significant rate of postoperative infertility, and, although this risk is improbable following trans-hysteroscopic surgery, there are necessary randomized studies regarding the benefits of surgery on reproductive performance.

The cervical incompetence (congenital or traumatically acquired, characterized by non-painful uterine cervical dilation, after 14 weeks of gestation, accompanied by prolapse and swell of the fetal membranes in the vagina, followed by the membranes rupture and expulsion of an immature fetus) is often cited as cause of late abortion [46, 47, 48].

As the diagnose of this discrete obstetrical entity (mainly based on the painless late abortion history) is not supported by a precise objective method (outside pregnancy, the suspicion appears when it is observed a larger internal cervical orifice, and during pregnancy, by ultrasound dynamic detection of the quasi typical cervical modifications [49, 50]), it is believed that often it is used excessively, one of the evidence being the modest reduction of the incidence of late abortions consecutive to the application of the cervical cerclage [51, 52, 53, 54, 55].

Excessive diagnose of cervical incompetence is demonstrated also by the results of a study (presented by the Rai group [22]) conducted on 208 late abortions, that identifies in 49% of cases the fetal death as cause of the abortion, in 19% of cases the expulsion of the conception product being preceded by painful uterine contractions and uterine bleeding, and only in the remaining third of cases the abortion was preceded by the spontaneous rupture of the membranes; it is only in this last group that a possible diagnose of cervical incompetence can be suspicioned.

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 septicemia 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) [56].

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 [57, 58, 10, 59, 60, 61].

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 [62], 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 [63], while values of CRP < 2mg/dl indicate the absence of chorioamnionitis for the following 25 hours in 98% of preterm ruptured membranes [64].

II. 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 postabortum (the release at 72 hours postabortum not identifying a pathology connected to the abortion, reconfirmed ambulatory after the first menstruation).

d) 12 pregnant women in the second trimester with threatened abortion of unknown cause, but who didn't evolve towards spontaneous abortion during the hospitalization;

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 [20]);

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 coagulaso-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 [65].

III. Results and Discussions

The results of our study are depicted in tables I and II.

As in case of the non-complicated postpartum [62] our results (table I) 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.

Table I. Demographic characteristics, CRP and no of serum leukocytes/ml of the studied groups pre and post late abortum without complications

Group		A. Second trimester pregnancy with fetal complications that impose medical induction of abortion (with intravaginal prostaglandins)	B. Second trimester pregnancy complicated with threatened abortion that evolved after 72 hours from check-in with the spontaneous expulsion of the conception product	A+B. 13-27 weeks pregnancies with non-complicated postabortum evolution, spontaneous or induced
Number		10	7	17
Age		23,7±1,7	26,57±3,53	24,88±1,73
Parity		1,3±0,66	1,7±0,69	1,47±0,49
Gestational age (weeks)		21,5±1,33	22,8±1,67	22,05±1,02
CRP mg/dl [no leukocytes / ml]	Preabortum	1,35±0,36	0,72±0,06	1,09±0,26 [1156±289]
	24 (12) hours postabortum	*3,31±0,55	*2,42±0,63	*3,22±0,38 (2,6±1,06) [8816±533 (8300±828)]
	48 (36) hours postabortum	2,7±0,52	1,55±0,95	2,42±0,46 (2,75±0,15) [7660±790 (7033±1256)]

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 postabortum and concords with prior observations on this relation, both postpartum [62] as well as outside of the pregnancy [66, 67].

Table II. Demographic characteristics, CRP and number of leukocytes/ml of the second trimester of normal and complicated pregnancy studied groups

Group	Normal pregnancy	Threatened abortion	Pregnancy after at least 3 consecutive spontaneous abortions in history	Pregnancy complicated by urogenital infections
No	18	12	10	18
Age	21,7±0,91	23±0,96	25±0,09	23,88±1,52
Parity	0,33±0,13	0,41±0,19	0,1±0,1	0,72±0,39
Gest. age (weeks)	21,6±1,07	15,08±2,3	18,2±1,34	20,2±0,86
CRP: mg/dl	0,94±0,06	1,22±0,17	1,35±0,36	*3,83±0,65
No of leukocytes / ml (limits)	7156±289 (5400-9800)	6754±352 (4200-8500)	6960±410 (5000-8500)	7572±403 (4600-10400)

Table II 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.

IV. 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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