Histopathologic exam of the placenta, membranes and umbilical cord – essential step in orienting the standard complex investigation of recurrent abortion

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Abstract—Numerous morphopathological observations of the placenta, membranes and umbilical cord detect the ascending intrauterine infection and the placental vasculopathy as being dominant in the etiopathogeny of preterm labor. When it is possible to exclude the vasculopathy early, in the asymptomatic phase of the intrauterine infection by means of precise and rapid tests, such as serum C-reactive protein dosing, it results the necessity of routinely performing the histopathologic exam of the conception product, as an essential step of orienting the standard complex investigation of the recurrent abortion.

The thrombophilia defects can generate either extended placental thromboses or defects of placentation and embryonic implantation. It is thus necessary to introduce in the standardized investigation of the recurrent abortion the repeated screening for resistance to activated C protein, the molecular diagnosis for Leiden mutation of coagulation factor V, antithrombin III dosing, protein C and S concentrations, factor XII, the fibrinogen, the plasminogen, the normality of the fibrin plate lysis, congenital or acquired hyperhomocysteinaemia and to demonstrate in the laboratory the antiphospholipid antibodies that are persistent in the peripheral blood.

Keywords—abortion, thrombophilia, chorioamnionitis, C-reactive protein, histopathology.

I. INTRODUCTION

The abortion constitutes the most frequent complication of a pregnancy (affecting 15% of gestations [1]), and it's financial and emotional impact becomes considerable in the situation of recurrent abortions (defined as the loss of at least three consecutive pregnancies [2]) which, in 20% of cases are appearing in the second gestational trimester [3]. Nonetheless, in 1995, Wolf and Horger [4] focus the community’s attention on the necessity of a standardized investigation of recurrent abortion.

II. ANALYSIS AND DISCUSSION


Numerous morphopathologic observations of the conception product are systematically detecting, but in various proportions, both in late abortion as well as in preterm labor (that are overlapping, between weeks 20 to 28 of the gestation [12, 13]) the placental ischemia (fig. 1) and/or the acute amniochoriodecidual inflammation (fig. 2) as the most frequently involved pathological processes in the multifactorial and little understood etiology of the preterm labor [14, 15, 16, 17, 18].

Fig. 1 Old placental infarction. Large areas of accelerate aging of chorioic villi that appear abnormally small, avascular, with intense sclera hyalinization. (Hematoxylin-Eosin; ob.10)

Romero and collaborators [5, 6] reach the conclusion that in preterm labor, with or without premature rupture of membranes, the histopathologic examination of the placenta is a valuable and non-invasive screening for the possibility of microbial invasion of the amniotic cavity, because, systematically, severe subclinical acute chorioamnionitis, funiculitis and umbilical vasculitis, as well as the marginal or
mixed inflammation of the choriodecidua are tightly correlated
to the positive culture of the amniotic fluid obtained via
amniocentesis (fig. 3, fig. 4).

Fig. 2 Acute chorioamnionitis. Polyploid aspect of amniotic
membrane with rich inflammatory exudates in the chorioamniotic
axe; edema and exudates in the capsular deciduas - the severity of the
amniochoriodecidual granulocyte reaction suggests just like the acute
marginal choriodecidual inflammation the ascending intrauterine
infection (Hematoxylin-Eosin; ob.10)

Fig. 3 Umbilical vasculitis. Acute intravascular and intraparietal
inflammatory exudates, parietal edema. Umbilical vasculitis, as
funiculitis, is an indicator of maximal specificity (higher positive
predictive value) of microbial invasion of amniotic cavity
(Hematoxylin-Eosin; ob.20)

Fig. 4 Acute inflammation of the chorial board (Acute placentitis)
is the most sensitive indicator (higher negative predictive value) of
microbial invasion of amniotic cavity (Hematoxylin-Eosin; ob.20)

Bernal and team [15] show that prevention of preterm labor
complicated with chorioamnionitis is difficult, because
numerous medical and socio-economic predisposing factors
exceed the obstetrician’s control possibilities, suggesting, on
the other hand, that early diagnosis of chorioamnionitis in
pregnant women with preterm labor, by means of rapid and
precise tests, that should be developed (for instance, CRP [19,
20, 21, 22, 23]), followed, as early as possible, by an adequate
treatment with efficient antibiotics and strong and side effects
free anti-inflammatory could stop the preterm labor with a
considerable improvement of the perinatal mortality.

According to Burns group [24], the relation infection-
recurrent abortion is a current active research subject in order
to establish if there is a connection between the inherited
predisposition for the infection and the recurrent abortion
(including the second trimester) or if it is possible to delegate a
strong association between specific groups of vaginal bacteria
and the pregnancy prognosis [5, 7, 11].

The vaginal infections role causing recurrent preterm labor
is a new area of research [25] that seems to orientate with
predecision on the vaginal bacteriosis, defined as the
alteration of the vaginal flora, where the number of the
lactobacillus which usually predominate, is very low or they
are absent [26, 27].

Arias and co-authors [7], in accordance with Spong and
collaborators [11], are mentioning that 70% of preterm labors,
with or without premature rupture of membranes, are the result
of ascending intrauterine infection and placental vascuopathy.

As the Arias group [7], Rai and collaborators [9, 10], and
also Dizon-Townson and co-researchers [28] are suggesting
that the histopathologic examination of the placenta, which
reveals a infarction like placental vascuopathy expanded to
over 10% of the surface, with or without calcifications [29]
and/or accelerated and unequal maturation of the placental villi
next to multiple syncytial nodes, possibly the lack of
adaptation of the decidual spiral arterioles, represents a useful
screening in recurrent late abortions, preterm labor,
preeclampsia and growth delay or fetal death in the uterus.

In addition, the same three groups of researchers, in
accordance with observations of the utero and fetoplacental
arterial flux via ultrasonography [30], agree with the
possibility that the deficiency of the trophoblast to produce
adaptive modifications in the spiral arterioles is the cause of the
inadequate and unequal utero-placental blood flow that
would constitute the basis of both the accelerated maturation,
with numerous syncytial nodes and fibroses of the placental
villi and placental infarctions, of various intensities, knowing,
on the other hand, that thrombophilic defects [10] can generate
either extended placental thromboses or placentation and
embryonic implantation defects.

According to H. Marret and collaborators [31], the
thrombophilias can be acquired (primary and secondary anti
phospholipid syndromes, nephrotic syndromes), congenital
(quantitative and qualitative constitutional deficits in the
natural inhibitors of coagulation: C and S protein and
antithrombin) or mutations that pose an interest to the target
factors of these inhibitors and prevents their action: factor V
Leiden and that of the prothrombin or G202A10 mutation. To these one can add some of the more complex anomalies such as hyperhomocysteinaemia.

The Quinn group [32] observes the fact that the human infection with Ureaplasma urealyticum is capable to induce the appearance of antiphospholipid antibodies which are responsible for thrombotic placental lesions (by reducing the placental syncytiotrophoblast annexin [24] fig. 5).

![Fig. 5 Placental infarction. Fibrinoid necrosis near the atrophic villi with intense sclero-hyalinization focus, marked calcification – the last suggesting the possible aggression by antiphospholipid antibodies type IgM (Hematoxylin-Eosin; ob.10)](image)

The autoimmune explanation for a suggestive proportion of recurrent abortion, not rarely complicating the second trimester of pregnancy, is unanimously accepted today, on the basis of the primary antiphospholipid syndrome which refers to the association of recurrent abortions to venous thrombosis, with the demonstration in the laboratory of the antiphospholipid antibodies persistent in the peripheral blood [33, 34].

The sanguine screening for antiphospholipid antibodies is usually repeated in the first weeks of pregnancy for the fact that some women with recurrent abortions present abnormal results in this test only during gestation [1].

The resistance to activated C protein is the most studied thrombophilic defect nowadays, following the primary antiphospholipid syndrome, in the genesis of recurrent abortion, which affects with predilection the second gestational trimester [35].

The resistance to the anticoagulant effects of the activated C protein is autosomal dominantly inherited and is recognized as being the most important cause of venous thrombosis (with a prevalence of up to 60% among people with venous thrombosis) and familial thrombophilia [9].

In over 90% of resistance to activated C protein cases, the cause is represented by a "single point" mutation (Glutamine-Arginine) at the nucleotide in position 1691 in the coagulation factor V gene (Leiden mutation of factor V), and the factor V with the Leiden mutation is resistant to inactivation through the activated C protein (which, normally, cleaves and inactivates the factors Va and VIIIa, in the presence of the cofactor – the S protein), which leads to the generation of increased quantities of thrombin and implicitly to a state of hypercoagulability [3].

Starting from the data provided by the literature of specialty, drawing the attention both on the placental thrombotic etiology of late abortion [15, 7, 9], as well as on the large prevalence of the resistance to activated C protein among those affected by venous thromboembolic disease, Rai and collaborators [10] investigated the association of activated C protein resistance to late abortion.

The results for this investigation of the Ray group [10] show a prevalence of activated C protein resistance significantly larger among women with recurrent late abortion in priors, with respect to those with repeated abortion in the first trimester, as well as to those from the control group. The authors conclude that these results suggest that the resistance to activated C protein can be an important mechanism of late abortion, possibly connected to the intravascular hypercoagulability which accompanies the pregnancy, knowing that the activated C protein resistance is developed during pregnancy as a part of the normal hemostatic modifications of the pregnancy, which makes women with activated C protein resistance, preceding the pregnancy, develop an even more accentuated activated C protein resistance once the pregnancy installs and evolves with time.

Rotmensch and collaborators [35] indicate the necessity of introducing, in the standardized investigation of the recurrent abortion, of the repeated screening for the activated C protein resistance, alongside the molecular diagnosis for the Leiden mutation of the coagulation factor V.

![Fig. 6 Umbilical vein thrombosis. Endothelial lesions. Parietal edema (Van Gieson; magnifier)](image)

The Rai group [9, 10] completes the list of thrombophilic defects exploration with the dosing of antithrombin III, of C protein and of S protein (total and free) concentration, of factor XII, of fibrinogen, plasminogen and of the normality of the fibrin plate lysis, but also of acquired or congenital hyperhomocysteinaemia (rapidly correctable by means of folic acid supplements), which, although much rarer than the antiphospholipid antibodies and resistance to activated C protein are nowadays more and more frequently associated to the second trimester abortion via extended placental infarction. Dizon - Townson and the co-researchers [28] mention, nonetheless, that 42% of the placentas with over 10% of the surface infarcted reflect the fetus’s state of carrier of the factor V Leiden mutation (the most frequent genetic predisposition to
thrombosis, often marked by the umbilical blood vessels thrombosis, alongside extended placental infarction – fig. 6).

III. CONCLUSIONS

The fact that the etiopathology of late abortion and preterm birth is dominated by the placental vasculopathy and by the ascending intrauterine infection, in the conditions of the possibility of excluding the vasculopathy as early as the asymptomatic phase of the intrauterine infection, by means of the serum CRP screening, focuses the attention to the necessity of routinely applying, in case of late abortion and preterm birth, of the histopathologic exam of the conception product, as an essential step of orientation of the standard complex investigation of recurrent abortion, which would allow not only important economies of funds, time and emotions for the maternity and the affected families, but also the application of modern, preventive and curative therapy in the early stages of preterm labor, when, evidently, the systematic classical tocology appears superfluous.

Because of the large percentage of extended placental thromboses which are caused by the Leiden mutation of factor V, the most frequent genetic predisposition to venous thromboses, it is necessary to adopt as early as possible, in the investigation of the etiology of late spontaneous abortion, the exploration of the activated C protein resistance, which once detected in case of a patient with abortion, especially a recurrent one, imposes the exploration of her relatives, thus increasing efficiency, not only in fighting recurrent abortion by starting the antithrombotic therapy before conception, but also the risk of thrombosis in the general population.

REFERENCES


