Morphopathological changes induced by the Obstetrical Antiphospholipid Antibody Syndrome in fetal adnexa and uterus

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Abstract
The Obstetrical Antiphospholipid Antibody Syndrome (OAAS) is representing a separate entity of the global Antiphospholipid Antibody Syndrome (APS), focusing the pregnancy morbidity. OAAS is generating morphopathological changes in almost all components of the gestational biologic transitory system (GBTS): placenta, umbilical cord or uterine wall. The most important, serious and lengthened anomalies are occurring in placenta. Our research has been developed on a group of 68 patients diagnosed with OAAS, initially using the Sapporo criteria and later using the “Sydney” ones. There have been morphopathologically examined: placenta, umbilical cord and myometrium. Histological examination revealed on one hand macroscopic modifications: fibrinoid deposits, white or red placental infarctions, intervillous thrombosis, marginal or basal decidua hematoma, calcareous deposits, umbilical cord thrombosis, and on the other hand microscopic findings: placental infarction, fibrinoid necrosis, myometrial thrombosis, degenerative myometrial disorders, focal myometrial necrosis, villous stasis and necrosis, umbilical cord thrombosis. Because of the increased prothrombotic background, in APS, any vessel or organ could be involved, with no exception for GBTS elements. The basis of the pregnancy morbidity from the obstetrical APS is represented by the morphopathological changes occurring in fetal adnexa and uterine structures.

Keywords: placenta, umbilical cord, myometrium, morphopathological changes.

Introduction
Antiphospholipid antibody syndrome has been firstly and completely described in 1983 by Graham RV Hughes. APS is the most important and frequent prothrombotic condition involving all surgical or nonsurgical branches [1].

The Obstetrical Antiphospholipid Antibody Syndrome has been recently described as a separate unit of the APS, being characterized by the pregnancy morbidity: fetal death after the 10th gestational week, three or more spontaneous abortions before the 10th gestational week with maternal anatomic or hormonal abnormalities and paternal/maternal chromosomal causes excluded, severe preeclampsia or eclampsia, recognized features of placental insufficiency, intrauterine growth restriction, thromboembolic status pregnancy-related, a decrease in the success rates for the in vitro fertilization, one or more premature births of a morphologically normal neonate before the 34th week of gestation [2].

The morphopathologic background of these aspects is represented by a large variety of placental and umbilical cord injuries on one hand, and myometrial disorders on the other hand.

Material and methods
Our research has been developed between 2004–2007, on a group of 68 women diagnosed with Obstetrical Antiphospholipid Antibody Syndrome. Initially we have been using the Sapporo diagnostic criteria, but starting from December 2005 we are diagnosing and classifying OAAS using the revised classification criteria or “Sydney” criteria [3].

Clinical criteria
1. Vascular thrombosis – one or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity
   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th...
week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia, or (ii) recognized features of placental insufficiency, or
(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

**Laboratory criteria**

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of *The International Society on Thrombosis and Hemostasis*.

2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

3. Anti-β-2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met [3–5].

We have microscopically examined samples of: placenta, umbilical cord and myometrium. All of the samples have been acquired after birth (term or preterm birth, cesarean section or vaginal delivery). Myometrium has been sampled only by cesarean section.

**Results**

Our research is spotlighting the following morphopathologic findings:

Macroscopic modifications: Fibrinoid deposits – 28 cases (41.17%). Fibrinoid deposits are occurring in normal pregnancies also, as the birth term is approaching. These modifications are representing placental villosities agglutinated by the fibrinoid substance, obliterating intervillous area. The clinical outcome for these changes is represented by the functional exclusion of the affected placental areas.

White or red placental infarctions – 65 cases (95.58%) (Figure 1). Placental infarction could come into view for the normal pregnancies also, but in this case, the affected areas are not exceeding 5% of the placental area. In placentas from patients with OAAS the placental infarction could interest 20–30% from the placental surface. There are cases as for the catastrophic APS when the infarcted area is extended in the entire placental body [6].

Intervillous thrombosis – 42 cases (61.76%). A mixture of maternal and fetal blood is coagulating, limiting the excessive transfer of the maternofetal blood. Marginal or basal decidual hematoma – eight cases (11.76%). There are hematomas situated in basal decidua, having retro-placental progression.

Calcereous deposits – 52 cases (76.47%) (Figure 2) – being visible on the maternal face of the placenta, as granularly deposits of calcium and magnesium carbonates and phosphates.

Umbilical cord thrombosis – 19 cases (27.94%) – could occur in any of the umbilical vessels. If there is extensive thrombosis, or association between thrombosis and umbilical cord hematoma, *in utero* fetal death could come off.

Microscopic changes: placental infarction – 67 cases (98.52%) (Figures 3 and 4) – is characterized by progressive degeneration of all villously structures because of the disappearance of the intervillous space. Fibrinoid necrosis – 30 cases (44.11%) (Figure 5) – fibrin deposition occurs in damaged and necrotic vessel walls.

Myometrial thrombosis – 11 cases (16.17%), degenerative myometrial disorders – 13 cases (19.11%) (Figure 6), focal myometrial necrosis – 5 cases (7.35%), villous stasis and necrosis – 39 cases (57.35%) (Figure 7), umbilical cord thrombosis – 26 cases (38.23%). Even if the myometrium is not actually an element appertaining to GBTS, thrombosis and necrosis are occurring because of the high prothrombotic condition from APS.

From the obstetrical point of view, we have had the following outcome: 64 live births (94.11%) and four fetal losses (5.88%). Three of the fetal losses were premature births, aged between 29–33 weeks of gestation. One fetal loss at 37 gestational weeks. Fifty-three of the newborns have had a favorable neonatal evolution. Only one neonate has been diagnosed with hydrocephalia, debuting later postpartum. There has been not diagnosed any correlation between OAAS and fetal hydrocephalia. There have been 49 term births (72.05%) and 19 preterm births (27.94%).

Intrauterine growth restriction (IUGR) has been diagnosed in 24 cases (35.19%). In our study group, there were 66 singleton pregnancies and two twin pregnancies (1-twin to twin transfusion syndrome – TTTS). The therapeutic skills that we have fulfilled included low-dose aspirin (75 mg/day), including preconceptional administration + heparin (5000 UI/12 hrs. when the pregnancy is confirmed) [2, 7–9].

As a characteristic of the OAAS, administration of warfarin is prohibited in pregnancy because of its teratogenic effects and fetal hemorrhages [2, 7].

In our research, we have been diagnosing easy or medium forms of preeclampsia for seven cases out of 68 (prevalence of 10.29%). When preeclampsia is diagnosed in association with OAAS, pregnancy morbidity is increased. There has been proven the association between APS and preeclampsia, eclampsia and HELLP syndrome. The physiopathologic background of this association is represented by the vascular disorders occurring in fetal adnexa and uterus [2, 7, 10].
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Figure 1 – Macroscopic modifications – white and red placental infarctions

Figure 2 – Macroscopic modifications – calcareous deposits

Figure 3 – Microscopic modifications – placental infarction (HE staining, ×40)

Figure 4 – Microscopic modifications – placental infarction and calcareous deposits (HE staining, ×100)
Figure 5 – Microscopic modifications – fibrinoid necrosis (HE staining, ×200)

Figure 6 – Microscopic modifications – degenerative myometrial disorders (HE staining, ×400)

Figure 7 – Microscopic modifications – villous stasis (HE staining, ×100)

Figure 8 – TTTS – mummified fetus and placenta
The Obstetrical Antiphospholipid Antibody Syndrome is nowadays diagnosed and classified according to the international consensus statement or “Sydney” criteria, that includes two clinical criteria (vascular thrombosis, pregnancy morbidity) and three laboratory criteria (lupus anticoagulant, anticardiolipin antibody, anti-β2 glycoprotein-I antibody) [3, 11, 12]. The new diagnostic criteria for APS are improving the old Sapporo criteria, adding one more laboratory criterion: anti-β2 glycoprotein-I antibodies [13, 14–17]. For our research, 40 cases have been diagnosed using Sapporo criteria and 28 using the new revised ones.

According to the international consensus for classification of the APS, our study group is divided as it follows: APS type I (clinical criteria + more than one laboratory criterion present – any combination) – 11 cases (16.17%); APS type IIa (clinical criteria + LA present alone) – 10 cases (14.7%); APS type IIb (clinical criteria + aCL antibody present alone) – 31 cases (45.58%); APS type IIc (clinical criteria + anti-β2-GPI antibody present alone) – 16 cases (23.52%). APS type IIb is frequently associated with significantly increased pregnancy morbidity [18, 19–21]. APS type IIc seems to have the lowest rate of obstetrical manifestations [2, 22, 23].

Three neonates died post-partum due to prematurity complications. For the case of fetal loss at 37 gestational weeks, there have been recognized features of placental insufficiency [24–26]. For one of the twin pregnancies TTTS has been diagnosed. The obstetrical outcome for this case was the following: one living fetus (1680 g) and one dead, mummified fetus (Figure 8). For the other twin pregnancy the fetal outcome was favorable: both living neonates (2830 g and 1490 g) with favorable neonatal evolution.

In APS, any vessel or organ could be involved, with no exception for GBTS elements. The background for the clinical manifestations from the obstetrical APS is represented by the morphopathologic modification axis: thrombosis-infarction-necrosis.

The most important, serious and lengthened morphopathologic changes are occurring in placenta. Placental infarction is the most frequent histological modification, followed by calcareous deposits, intervillous thrombosis and villous stasis and necrosis. The most common of the morphopathologic changes occurring in the umbilical cord in OAAS is thrombosis. Myometrium is oftentimes affected in APS by myometrial thrombosis, degenerative myometrial disorders or focal myometrial necrosis.

APS IIb is the most frequent type of syndrome in our research and it is associated with significantly increased pregnancy morbidity. Preconceptional use of aspirin is very important because of its antithrombotic effect. Therapy for the obstetrical APS is quite simple and efficient, in opposition with the clinical manifestations.


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