Postpartum hemorrhages

Abstract

Although any pregnant woman can be considered at risk for peripartum bleeding, the degree of risk is suggested by various medical and obstetrical factors. Preexisting coagulation disorders caused by hematological or systemic diseases, the therapeutic use of anticoagulants, anemia and nutritional deficiencies are some of the predisposing medical factors to which obstetrical factors such as uterine atony, abnormal placentation, obstetrical trauma and peripartum coagulopathy can be added. A number of high-risk entities, the most complex of which is coagulopathy, stand out among the numerous factors which contribute to the ever-present risk of peripartum hemorrhage. Obstetrical complications are patho-physiologically enmeshed with the adaptive changes which take place during pregnancy. Coagulopathies act either as a morphological substrate or a complication of obstetrical emergencies such as small and frequent, or, conversely, abundant hemorrhages, obstetrical shock from prolonged labor, retention of a dead fetus, important third-trimester dysgravidia, placental abruption or amniotic fluid embolism. Hemostasis differ between pregnant and non-pregnant women. The adaptative changes in hemostasis during pregnancy are mainly attributed to the higher level of estrogens and affect a number of concurrent elements: vascular capacity, platelet function, serum levels of the coagulation factors and fibrinolysis. Although changes in plasma factors, thrombocytopenia and alterations in blood flow do not alter hemostasis during pregnancy, labor or the puerperium, they may reveal the presence and/or aggravation of certain illnesses which are associated with or induced by pregnancy. Protective endothelial mechanisms and molecules such as antioxidants, natural antiaggregants and the balance between prostacyclin and endoxane have been described in normal pregnant women. The main causes of postpartum hemorrhage are uterine atony, abnormal placentation, obstetrical trauma, acquired coagulopathies and illnesses associated with and specific to pregnancy which are accompanied by coagulation disorders. In the present review, further inside in the coagulation disorders which accompany amniotic fluid embolism, dead fetus retention, sepsis, maternal hypertension, premature detachment of a normally inserted placenta and obstetrical trauma is presented. Moreover, bacterial endo- and exo-toxins and the antibody-antigen complexes produced in sepsis act as a trigger for disseminated intravascular coagulation is described.

Keywords: *uterine atony, abnormal placentation, obstetrical trauma, peripartum coagulopathy*

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Introduction

A number of high-risk entities, the most complex of which is coagulopathy, stand out among the numerous factors which contribute to the ever-present risk of peripartum hemorrhage.

Hemorrhage represents the direct cause of death in 47.8% of all obstetrical deaths in Romania[1,2], and is the primary cause of maternal death in developed countries[1,2,3]. It is worth mentioning that 41.8% of deaths were due to postpartum hemorrhage and that uterine rupture was incriminated in 18.6% of all cases.

Coagulopathies act either as a morphological substrate or a complication of obstetrical emergencies such as small and frequent, or, conversely, abundant hemorrhages, obstetrical shock from prolonged labor, retention of a dead fetus, important third-trimester dysgravidia, placental abruption or amniotic fluid embolism[4]. These complications are pathophysiologically enmeshed with the adaptive changes which take place during pregnancy. The limit between the two is seldom very clear and the treatment is therefore often tailored to the effect and not to the cause, which can be obscure or impossible to determine. This can in turn lead to professional losses and errors.

Hemostasis differs between pregnant and non-pregnant women. The adaptive changes in hemostasis during pregnancy are mainly attributed to the higher level of estrogens and affect a number of concurrent elements: vascular capacity, platelet function, serum levels of the coagulation factors and fibrinolysis[4,5,6].

The platelet count, volume and lifespan remain unchanged in most pregnancies. A slight raise in platelet turnover at the level of the fetoplacentary unit is possible in some cases, which in turn leads to a slight drop in platelet count in pregnant women without a history of thromboctyopenia, especially during the third trimester of pregnancy. Conversely, platelet activity and release of vasoactive mediators are increased during the repair of the uteroplacental unit, as well as in relation to some of the complications of pregnancy[4,7].

The circulating levels of the coagulation factors suffer a number of changes during pregnancy. An elevation of the serum levels of fibrinogen, factors VII, VIII, X, XII, XIII and von Willebrand factor appears during trimesters II and III. Factor XI is decreased during pregnancy, whereas the serum levels of factor IX and III are either slightly increased or remain unchanged. The circulating levels of the coagulation inhibitors are also altered during pregnancy: antithrombin is either slightly decreased during the third trimester and postpartum period or remains unchanged, protein C may either remain unchanged or be slightly increased, protein S levels (particularly those of its free fraction) are decreased, lower levels of plasma activity are present during the last two

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trimesters and persist until 6-8 postpartum, tissue factor plasma inhibitor suffers a significant increase during pregnancy, thrombomodulin is increased and so is activated protein C resistance.

The values of the coagulation tests used in the evaluation of hemostasis (prothrombin time, activated partial thromboplastin time, international normalized ratio and thrombin time) are slightly decreased during pregnancy, due to elevated factor VIII levels[8,9].

The factors which modulate fibrinolysis may also suffer some changes during pregnancy. Plasminogen levels either remain unchanged or become slightly elevated, tissue plasminogen activator (PA) and urokinase-PA levels decrease during the first 10 weeks of pregnancy, then suffer a significant increase during the second and (particularly) the third trimester and fibrinolysis inhibitors are markedly increased during pregnancy. The levels of plasminogen activator inhibitors (PAI)-1, produced by endothelial cells and PAI-2, whose synthesis depends on the placenta, rise progressively throughout pregnancy. Their values return to normal at 6 weeks postpartum. Thrombin-activated fibrinolysis inhibitor levels are high during pregnancy, reaching their peak during weeks 35-39 and subsequently suffering a rapid decline 24 hours postpartum[4,9].

Hemostasis markers are altered during pregnancy, reflecting the increasingly generated quantities of thrombin (i.e. prothrombin fragments 1 and 2, and fibrinopeptide A) and the rise in fibrinolysis (i.e. D-dimers, PAP complexes)[4,9].

Platelets and coagulation factors become activated and are subsequently consumed during parturition and uterine contractions. Raised levels of D-dimers indicate a concurrent increase in fibrinolysis, including PAP complexes.

Immediately after childbirth, the modified levels of the coagulation factors go through a progressive decrease and revert to their original values at 4-6 weeks postpartum, with the exception of protein S, whose low levels persist until 8 weeks after birth. The plasma factors which are involved in fibrinolysis decrease rapidly after birth (in 24 to 48 hours), with the exception of PAI-2, whose high values persist for 8 weeks postpartum[8,9].

Coagulation disorders in pregnancy

Although changes in plasma factors, thrombocytopenia and alterations in blood flow do not alter hemostasis during pregnancy, labor or the puerperium, they may reveal the presence and/or aggravation of certain illnesses which are associated with or induced by pregnancy.

Protective endothelial mechanisms and molecules such as antioxidants, natural anti-aggregants and the balance between prostacyclin and endoxan have been described in normal pregnant women[4].

Coagulation factor deficits, hypocoagulability and hemorrhagic syndromes are interconnected, but not super-imposable. The deficit of one factor may either become compensated or may lead to a state of hypocoagulation. The same clinical picture can be produced by a deficit of one or more factors. Furthermore, the same etiology can lead to a deficit of several factors and distinct etiologies can lead to a deficit in one given factor[4].

Etiopathogenesis of obstetrical hemorrhage

The severity of obstetrical hemorrhage is due to the following facts[7,10]:

- the debit of the uterine artery progressively increases during pregnancy, reaching 600 mL/min at term; a large quantity of blood may therefore be lost in very little time in the case of an obstetrical hemorrhage;
- relatively small but recurrent and persistent blood losses can lead to a precarious hematological and hemodynamic balance in pregnant women, which can rapidly evolve towards hemorrhagic shock if the blood loss repeats itself;
- a super-imposed coagulopathy exacerbates any given hemorrhage; this is almost a rule in the case of obstetrical hemorrhage due to:
  - ✓ the state of hypercoagulability characteristic of pregnancy, where any hemorrhage may lead to disseminated intravascular coagulation (DIC);
  - ✓ specific obstetrical causes, which are accompanied by coagulation factor abnormalities;
  - ✓ an excessive loss of coagulation factors which accompanies blood loss;
  - ✓ the dilution of the remaining coagulation factors upon repletion of circulating volume;
  - ✓ release of tissue thromboplastin from injured structures.

Causes of postpartum hemorrhage

The principal causes of post-partum hemorrhage are uterine atony, abnormal placentation, obstetrical trauma, acquired coagulopathies and illnesses associated with and specific to pregnancy which are accompanied by coagulation disorders[7,11].

1. Uterine atony

- frequency: 1/20 births;
- the mechanism of blood loss is represented by the absence of efficient uterine retraction after delivery, leading to incomplete occlusion of the utero-placental arteries;
- clinical characteristics: soft uterus, difficulty in delimitating the fundus;
- significant risk factors include:
  - ✓ uterine overdistension *via* macrosomic fetus, polyhydramnios or multiple pregnancy; the overdistended myometrial fiber contains disorganized contractile proteins and therefore latently resumes its undistended state postpartum;
  - ✓ multiparous women, who have low-quality myometrial fibres which demonstrate areas of degeneration and fibrous repair;
  - ✓ prolonged labor or drawn-out oxytocin infusions which exhaust the myometrial fibers;

- ✓ obstetrical anemia, which affects the iron-dependent enzymes which assist with uterine contraction;
- ✓ rapid extraction of the placenta during caesarean section, which coincides with the refractory phase of myometrial contraction;
- ✓ a particularly strenuous situation is represented by the accumulation of blood clots in the uterus, with minimally exteriorized bleeding, which prevents retraction; in some cases, a consumptive coagulopathy via either the intrauterine clots or the loss of coagulation factors through exteriorised bleeding may be involved[7].

2. Anomalies of placental development and insertion

- ■ frequency: 1/2000 births;
- ■ the most important risk factors for the appearance of placental development and insertion anomalies are: multiparity, advanced maternal age, multiple pregnancies, previous abortions, and the presence of uterine scars;
- ■ hemorrhage may appear during pregnancy due to placental abruption, which rapidly distends the lower uterine segment and leaves the inextensible placenta in its wake[8];
- ■ hemorrhage may also appear during labor in:

A. Lateral placenta praevia *via* slippage of caduces (Schroder) or traction of the membranes (Pinard).

B. Central and partially central placenta praevia, where the dilation of the uterine orifice uncovers portions of the placenta, opening the intervillious spaces and leading to hemorrhage:

- ✓ a hemodynamic mechanism which is characteristic of placenta praevia contributes to the debut and perpetuation of hemorrhage, namely the difference between the higher blood pressure of the intervillious spaces and the considerably lower blood pressure of the cervical insertion of the placenta;
- ✓ another contributing factor is the dilaceration of the myometrial fibers of the inferior uterine segment from the chorial vilosities, thereby opening the vascular plexi of the plexiform layer of the myometrium;
- ✓ central placenta praevia is also associated with delivery hemorrhages due to its insertion into the lower uterine segment, which has few muscular fibers which cannot retract strongly enough to produce efficient "biological ligatures"[9].

C. Disorders of placental attachment (accreta, increta, percreta)

- ✓ the level of trophoblastic invasion is not limited, due to the incomplete development of Nitabuch's layer;
- ✓ when the placenta detaches, the abnormally adherent areas get in the way of normal myometrial contractility and prevent regular vascular occlusion, resulting in hemorrhage;
- ✓ coagulopathy often occurs with the bleeding and is increased by the resulting hypofibrinogenemia, due to massive tissue destruction and blood loss[10].

D. Premature detachment of a normally-inserted placenta

- ✓ incidence: 1/120 births;
- ✓ the mechanism behind the initial detachment is represented by a zone of inter-utero-placental hemorrhage with the formation of a retroplacental hematoma, which in turn displaces a larger placenta area, thereby initiating a vicious circle;
- ✓ the accompanying coagulopathy is due to the massive depletion of coagulation factors in the retroplacental hematoma;
- ✓ DIC phenomena are caused by the release of a placental thromboplastic factor into the bloodstream;
- ✓ the etiology is unknown;
- ✓ risk factors include: maternal hypertension, multiparity and a previous history[11].

3. Obstetrical trauma

- ■ the severity of the hemorrhage is determined by the surface, depth and location of the continuity solution[7,12];
- ■ risk factors include: inferior genital tract hypoplasia, large fetus, brutal or incorrect obstetrical maneuvers, the quality and elasticity of the mother's tissues, and the presence of previous scars which may influence tissue flexibility and amplification;
- ■ vaginal hematomas may appear without concurrent mucosal rupture *via* the ilacerations of the vaginal mucosa from the subjacent tissues due to its participation in the rotational movements of the presentation
- ■ the resulting hematoma dissects the two tissues from on another, amplifying the bleeding and the depletion of coagulation factors[12];
- ■ specific entities pertaining to obstetrical trauma include:

A. Uterine rupture

- ✓ risk factors include: prolonged labor, mechanical dystocia with cephalopelvic disproportion, multiparity, oxytocin perfusions, the presence of uterine scars[1,2,3];
- ✓ a large, dissecting hematoma appears due to the involvement of important vascular pedicles which open into the broad ligament; this leads to the perpetuation and aggravation of the resulting hemorrhage, with the rupture of multiple small-calibre blood vessels;
- ✓ the hemorrhage progresses into the retroperitoneum as hypovolemic shock develops and is in turn worsened by the retroperitoneal irritation which provokes;
- ✓ the resulting consumptive coagulopathy has two mechanisms: depletion of coagulation factors within the hematoma and release of tissue thromboplastin from the ruptured zone into the bloodstream[13].

B. Episiotomy

- ✓ a incorrectly sutured episiotomy in which the blood vessels located in the superior angle of the incision are overlooked can lead to the development

of hematoma which dissect into the ischiorectal fossa and/or the retroperitoneum, which can in turn lead to hypovolemic shock and consumptive coagulopathy[14].

C. Application of forceps

- ✓ the application of forceps can produce cervical lacerations which sometimes extend into the lower uterine segment, uterine rupture, vaginal rupture (which is sometimes spiroid or which may lead to the disinsertion of the vagina), formation of pelvic hematoma or extension of an episiotomy[15].

D. Caesarean section

- ✓ caesarian section may be associated with the loss of approximately 1000 mL of blood;
- ✓ risk factors include:
  - a necessary transplacental incision (in placentas with an anterior or low insertion or in placenta praevia) with difficult retraction of the lower uterine segment;
  - abnormal placental insertions, in which the dilaceration and distruction of myometrial fibers make uterine retraction more difficult;
  - lengthening of the initial incision with section of the uterine pedicles;
  - uterine atony.

4. Acquired coagulopathies

Several favorable conditions associated with pregnancy may lead to the development of a coagulation disorder: physiological hypercoagulation, large quantities of thromboplastin tissue which exist inside the uterus and placenta and which can be released into the bloodstream following local trauma, leading to DIC and the activation of fibrinolytic mechanisms[16].

Coagulation disorders accompany: amniotic fluid embolism, the retention of a dead fetus, sepsis, maternal hypertension, and obstetrical trauma. Bacterial endo- and exo-toxins and the antibody-antigen complexes produced in sepsis act as a trigger for DIC. Hypofibrinogenemia has also been known to accompany degenerate uterine leiomyomas associated with pregnancy, placenta accreta and ovarian thrombotic accidents associated with therapeutic anticoagulation[15].

The factors which can interfere with postpartum uterine hemostasis include:

A. Mechanical factors - the contraction and retraction of the uterus can be affected by the following factors:

- ✓ the presence of an intrauterine formation which prevents the uterine wall to revert to a smaller diameter, which is favorable to hemostasis:
  - placental retention via abnormal adherence or placental incarceration;
  - the presence of placental fragments within the uterine cavity;
  - uterine fibroids:
- ✓ insertion of the placenta onto the lower uterine segment, which has few myometrial fibers;
- ✓ the presence of an abnormally adherent placenta: placenta accreta, increta, percreta;
- ✓ various uterine malformations;
- ✓ the presence of uterine scars;
- ✓ exaggerated uterine distension through hydramnios or multiple pregnancy may influence uterine;
- ✓ retraction and contraction through the disaggregating of actomyosin bands;
- ✓ rapid uterine evacuation through forceps application or major extraction;
- ✓ prolonged administration (or overdose) of ocytocics;
- ✓ hypo- or hyper-kinetic labors;
- ✓ spontaneous or provoked uterine inversion;
- ✓ cervical, vaginal or perineal lacerations;
- ✓ uterine rupture[17].

B. Metabolical factors

- ✓ the myometrial cell is functionally affected by hypoxia, acidosis and low levels of glycogen;
- ✓ they are involved in the following clinical settings:
  - uterine hypo-perfusion in preeclampsia, vascular lesions, anoxia;
  - respiratory insufficiency;
  - ecompensated diabetes mellitus;
  - infections;
  - prolonged hyperkinetic labor;
  - drawn out oxytocin perfusions;
  - hypocalcemia due to endocrine disorders or administration of frozen blood products[18].

C. The administration of tocolytic drugs such as:

- ✓ beta-mimetics;
- ✓ magnesium sulfate;
- ✓ general anesthesia;
- ✓ analgesics;
- ✓ central nervous system depressors.

D. Coagulation disorders

- ✓ alterations in the synthesis of or quantitative deficits of the coagulation factors;
- ✓ vitamin K insufficiency;
- ✓ therapeutic anticoagulation;
- ✓ platelet deficits;
- ✓ aspirin (inhibits the cyclooxygenases).

E. DIC

- ✓ most often complicates of amniotic fluid embolism, dead fetus retention, chorioamniotitis, eclampsia[19].

5. Causes of hemorrhage during the third and fourth stage of labor

A. Bleeding at the level of the placental bed due to uterine atony or other placental causes

B. Obstetrical trauma of the genital tract

The presence of coagulation disorders amplifies all of the afore mentioned conditions.

6. Preexisting disorders of hemostasis

Some disorders of hemostasis which predate the pregnancy may appear in[16]:

A. Hematological syndromes: Fanconi anemia, aplastic anemia.

B. Hemorrhagic diatheses which involve several mechanisms which can coexist and/or interfere with one another:

- ✓ alterations at the level of the vascular wall (vasculopaties);
- ✓ quantitative disorders of platelets (thrombocytopenia or thrombocytosis);
- ✓ qualitative disorders of platelets (thrombastenia, thrombopathies);
- ✓ disorders of coagulation[20].

7. Pregnancy-associated illnesses which induce coagulation disorders[4]

A. Diseases of the liver

- ✓ the hemodynamic, rheological and hemostatic alterations of pregnancy are superimposed not only upon those caused by the liver disease itself, but also upon several changes in the vascular bed determined by the resulting hepatic insufficiency;
- ✓ the liver is a target effector or receptor in the pathophysiology of numerous diseases associated with pregnancy; it is therefore one of the first organs to be affected by any pathological state which leads to the inhibition of aerobic glycolysis pathways, irrespective of the etiopathogenic mechanisms involved[16];
- ✓ a number of anatomical factors, functional liver disorders and an array of liver disease complications may induce:
  - secondary thrombocytopenia via a decrease in protein synthesis;
  - a decrease in the absorption and metabolization of vitamin K;
  - functional deficits at the level of the monocyte-macrophage system[21].

B. Vascular nephropaties

- ✓ vascular nephropathies are accompanied by several coagulation disorders caused by the production of highly aggregate and adhesive abnormal platelets, but also by alterations of platelet factor III;
- ✓ the serum levels of fibrinogen and factors V and VIII are higher in nephrotic syndromes;
- ✓ kidney function is altered in septic shock as a byproduct of:
  - hemorrhage, which leads to hypovolemic hypoxia with vasoconstriction;
  - infection, which may lead to DIC, hemolysis, interstitial nephritis and papillary necrosis through the abnormal activation of several mechanisms of coagulation, leading to the appearance of fibrin deposits at glomerular level;
  - "Sanarelli-Schwarzmann phenomenon", in which fibrin deposits form within the capillaries of the glomerular tubules[22].

C. Disseminated *lupus erythematosus*

- ✓ is a conjunctive tissue disorder which affects several organs and also induces alterations at the level of the immune system
- ✓ the patient presents with normochromic or hemolytic anemia and/or thrombocytopenic purpura

D. Diseases of the hematopoietic system

a) Chronic myeloid leukemia

- ✓ patients present with altered hepatic function and improperly matured megakaryocytes;
- ✓ hematological tests indicate a low prothrombin concentration in the absence of prothrombin depletion and platelet dysfunction;
- ✓ hemorrhagic accidents are paradoxically infrequent[23].

b) Acute leukocytosis

- ✓ this disorder is hematological characterized by the presence of thrombcytopenia, platelet dysfunction, the absence of prothrombin consumption and a rise in the fibrinolytic activity of plasma in the final stages of the disease[24].

c) Malignant lymphogranulomatosis and other reticulocytoses

- ✓ the patient has a tendency towards hypercoagulation, with hyperfibrinogenemia and the presence of intermediate fibrinogen polymers.

E. Diseases of the spleen

- ✓ splenic disorders are often accompanied by hemorrhage, which is produced by two mechanisms: increased capillary fragility and thrombocytopenia.
- ✓ a tendency towards hypercoagulation (with or without thromboses) appears after splenectomy.

F. Lesions of the skin and muscles

- ✓ necrotic lesions caused by frostbite or crush syndrome release thromboplastin into the bloodstream and are therefore often accompanied by DIC[14].

G. Diseases of the pancreas

- ✓ patients with pancreatitis have a tendency to bleed out due to high levels of circulating trypsin and antithrombin[15].

H. Rheumatological diseases

- ✓ hypercoagulability and the presence of intermediate fibrinogen polymers are noted;
- ✓ low levels of factors II, V and prothromboplastin factors.

I. Diabetes mellitus

- ✓ hyperglycemia directly alters the vascular endothelium, as well as the fibrinolysis and coagulation mechanisms;
- ✓ platelets become hyperfunctional, with a rise in adhesion and aggregation as well as in the production of thromboxane and a decrease of endothelial prostacyclin synthesis;
- ✓ thrombogenesis takes place in areas with focal endothelial lesions, thereby intensifying hemodynamic stress[16].

J. Carcinomatosis

- ✓ carcinomatosis produces a chronic state of DIC through the widespread invasion of numerous tissues, leading to the release of tissue factors or to the direct activation of the prothrombinase complex by mucin or another neoplastic procoagulant factor.

K. Coagulation disorders associated with human immunodeficiency virus (HIV)

- ✓ the hematological manifestations of HIV have the following characteristics:
  - clinical and biological mononucleosis-like syndrome during the infection phase;
  - persistent lymph node involvement and frank thrombocytopenia during the intermediate phase;
  - severe hematological complications associated with tumoral syndrome in the active phase; autoantibodies such as the antiprothrombinase circulating anticoagulant factor appear frequently during this phase[25].

L. Complications of blood transfusions

- ✓ the only relevant complications in this context are the immunological reactions against erythrocytes (intra- or extra-vascular hemolysis), leukocytes, thrombocytes, immunoglobulins or other plasmatic antigens[16].

M. Coagulation disorders in infectious diseases

- ✓ thrombocytopenic purpura appears in rickettsioses;
- ✓ prothrombin and proconvertin levels go down by approximately 24-50% in septicaemias with *Pseudomonas sp.*, *E. coli*, *Proteus sp.*, *Klebsiella sp.* or *Enterobacter sp.*;
- ✓ hypothrombinemia and hypofibrinogenemia are associated in Staphylococcal septicaemias.

N. Trophoblastic tumors

- ✓ trophoblastic tumors interfere with the thromboplastinic system by secreting a host of placental proteins.

O. Chorioangioma

- ✓ chorioangioma is a vasculo-conjunctive tumor which resembles a hamatoma originated from blood vessels that have failed to establish a connection with the villous vasculature;
- ✓ it is associated with a rise in placental blood flow, hemolytic anemia and thrombocytopenia in the affected fetus.

P. Isoimmunisation during pregnancy

- ✓ tissue thromboplastin and plasminogen activating factor are released consecutive to haemolysis;
- ✓ defibrination occurs and antigen-antibody complexes produce endothelial lesions, leading to the release of coagulation antibodies[8,9].

8. Pregnancy-specific illnesses associated with coagulation disorders

The specific mechanisms pertaining to this category of coagulation disorders are: the release of active thromboplastin and infectious endo-toxins into the bloodstream, retention of procoagulant substances, the activation of factor XII and the presence of heparinic circulating inhibitor.

A. Preeclampsia

- ✓ preeclampsia is characterized by a abnormal function of vascular reactivity, abnormal coagulation and fluid balance, dysfunctions at the level of the kinine system and abnormal activation of prostaglandins;
- ✓ its origin is represented by utero-placental ischemia;
- ✓ the presence of hypertension worsens any endothelial lesions[10];

Preeclampsia may progress toward DIC or other similar coagulation disorders due to:

- ✓ the production of prostacyclines by widespread cellular endothelial lesions;
- ✓ platelet hyper-aggregation due to an imbalance between prostaglandin-2 and thromboxane A2;
- ✓ immediate release of trophoblastic thromboplastin;
- ✓ this small-scale form of DIC is biologically reflected by the appearance of changes in the number of platelets, the presence of serum PDF, a decrease of fibrin levels and a higher bleeding time
- ✓ high levels of thrombin cannot be entirely compensated for by normal quantities of antithrombin III, which is consumed faster than it can be produced. while any supplementary fibrin is metabolised by the plasmatic system, leading to the appearance of PDF and D-Dimers in the bloodstream;
- ✓ thrombocytes are precociously activated and rapidly depleted in preeclampsia[3,4,8,15].

B. Placental abruption

- ✓ placental abruption is a pregnancy-specific illness whose etiology is the subject of numerous obscure and contradictory theories;
- ✓ its evolution is unpredictable and may touch upon a whole pathophysiological range of conditions associated with pregnancy;
- ✓ the initiation, persistence and subsequent aggravation of vasospasm prevents any efficient intervention of vascular and hormonal regulatory mechanisms and is followed by metabolic imbalances such as acidosis, labored breathing, consumptive coagulopathy, hypoxia, multisystem organ failure, which worsen the patient's state and make therapeutic intervention almost impossible[7,8,10].

C. HELLP Syndrome

- ✓ HELLP syndrome is characterized by microangiopathic haemolytic anemia, hepatic cytolysis with elevated liver enzymes and low platelet count and is accompanied by clinical manifestation which resemble those of preeclampsia, with or without DIC;
- ✓ the underlying etiopathogenic mechanism is multifocal thrombotic and necrotic microangiopathy[3,8].

D. Postpartum haemolytic-uraemic syndrome

- ✓ clinical manifestations include hypertension, purpura and microangiopathic haemolytic anemia

- ✓ thrombocytopenia is inconstant;
- ✓ it is presumed to be caused by autoimmune haemolysis, as antiplatelet antibodies and circulating immune complexes are present[3].

E. Sheehan's Syndrome

- ✓ the clinical manifestations of Sheehan's syndrome resemble those of rapidly evolving and almost inevitably lethal liver failure;
- ✓ the associated coagulopathy mimics both primary DIC and other consumptive coagulopathies[3,26].

F. *In utero* fetal demise

- ✓ hemorrhage due to coagulation disorders is started by the release of coagulation activation factors such as thrombokinases into the maternal bloodstream, which brutally initiate the coagulation cascade;
- ✓ the aforementioned coagulation disorders are especially caused by hypofibrinogenemia, but also due to the rapid depletion of platelets and coagulation factors V and VIII;
- ✓ coagulation activation factors and thrombokinases enter the maternal bloodstream by effraction upon rupture of the membranes during parturition or delivery[8,10,11].

G. Amniotic fluid embolism

- ✓ appears in clinical situations which are associated with changes in the normal anatomic relationships between the chorioamniotic membrane, the placenta and the uterine wall;
- ✓ the integrity of the uterine blood vessels is compromised, allowing amniotic fluid to pass into the maternal bloodstream, where it has the following effects:

H. Coagulopathy after Caesarean section

- ✓ may be caused by postoperative anticoagulant therapy[18];
- ✓ numerous cases of amniotic fluid embolism in association with uterine rupture and Caesarean section have been described[5,7,10,11];
- ✓ the pathophysiology of amniotic shock can involve cardiogenic, anaphylactic or mixed pathways;
- ✓ coagulation disorders appear in patients that have survived for over one hour post-embolism;
- ✓ primitive fibrinolysis is presumed to be one of the therapeutic measures taken against the progression of hematological complications associated with amniotic fluid embolism (Beller, 1963)[4,8];
- ✓ associated with the presence of antithrombinasic anticoagulants and antibodies against coagulation factors V, VII, VIII, IX and XIII.

Conclusions

1. Obstetrical complications are extremely dramatic situations where therapeutic decisions are influenced by time, technical conditions, access to modern means of investigation and therapy. Most maternal and fetal deaths occur in these unfortunate circumstances.

2. Every medical specialist should have adequate knowledge of obstetrical pathology in order to efficiently and rapidly intervene in selected cases, if only by ensuring that the patient is directed to an adequate materno-fetal unit and transported there safely.

3. Each type of medical unit should be assigned to an adequate competence group, in order to avoid the potentially disastrous consequences of treating high-risk cases in poorly-equipped units.

4. Because pathological entities, particularly obstetrical ones, do not follow strict guidelines, all clinicians should be able to recognize important obstetrical disorders and their complications and knowledgeably intervene in such dramatic circumstances. ■

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