REVIEW ARTICLE

Obstetric Anesthesiology as the Third Pillar of Perinatology

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Abstract

Perinatology emerged in the second half of the 20th century when the examination, care, and treatment of the fetus as a patient became possible before and during birth with various biochemical and biophysical methods. The life functions of preterm newborn infants could be maintained with intensive care therapy. Nowadays, the health and the life of pregnant and puerperal women as well as their fetuses/neonates can dominantly be supported by professionals in obstetrics, neonatology, and anesthesiology. Perinatology combines collaborative efforts from obstetrics, neonatology, and anesthesiology, along with intensive therapy for caring about the life and health of the mother and the fetal/neonatal patients. In this volume, the third pillar of the triangle of perinatal care is emphasized. Participation of obstetrical anesthesiologists in the process of indication, mode of anesthesia, and timing of operative delivery is essential. Preeclampsia/eclampsia/hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and serious peripartum bleeding are the most common maternal and fetal life-threatening conditions, which require a high level of adult intensive care. The objective of this review is to prove the role of anesthesiology and intensive therapy as the third pillar of perinatal medicine in the management of great obstetrical syndromes.

Keywords: Anesthesiology, Definition of perinatology, Hemolysis, elevated liver enzymes, low platelet count syndrome, Intensive therapy, Neonatology, Obstetrics, Peripartum hemorrhage, Preeclampsia.

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Over the course of the last 60 years, obstetrics, which had remained virtually unchanged for centuries, has progressively emerged from the past to become a scientific discipline and perinatal medicine has been born. It has evolved from the cultivation of an art to a science.[1] Perinatal medicine did not begin to take shape until the beginning of the 1960s. In 1961, the first direct examination of the human fetus was carried out by taking blood samples from its presenting part during labor. Late in the 1960s, further events brought essential breakthroughs, namely when cardiotocography and ultrasonography were introduced on a broad scale, and suitable equipment became available for the first time for routine use. Armed with these new resources, specialists began to realize, for the first time, that the fetus could be considered a patient; their efforts focused on monitoring it during both pregnancy and birth itself. Until the 1960s, the fetus remained a genuinely unknown entity to both obstetricians and the medical world in general. Besides studying in a rudimentary fashion, its position inside the maternal claustrum, its approximate growth, and the presence of a fetal heartbeat, doctors were incapable of obtaining any other kind of fetal information. During these years, three prestigious personalities in this field have defined the limits of the subspecialty and published the first protocols—Erich Saling (Berlin), responsible for the introduction of biochemical (acid-base balance) control of labor,[2] Roberto Caldeyro-Barcia (Montevideo), who introduced the biophysical (electronic) control during labor,[3] and Ian Donald (Glasgow) introduced the ultrasound into the imaging methods of obstetrics.[4]

The term "neonatology" was coined by Alexander Schaffer, whose book on the subject, "Diseases of the Newborn," was first published in 1960.[5] This book, together with Clement Smith's "Physiology of the Newborn Infant"[6] formed cornerstones of the developing field. A body of specialized knowledge, a group of subspecialized professionals, the advent of technically advanced equipment, and the formation of special care units all contributed to the

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development of neonatology. These with similar elements in obstetrics resulted in the specialty of maternal–fetal medicine.[7] For pregnant women, the discipline of obstetrics starts with conception and lasts until the sixth week of the postpartum period. For pregnant women, the discipline of obstetrics starts with conception and lasts until the sixth week of the postpartum period. Neonatology takes over the care of the newborn infant until the postpartum sixth week. The perinatal period starts at the 24th week when the fetus already has a real chance to survive after birth;[8] thus, perinatology or perinatal medicine is the discipline for the perinatal period for both the mother and the fetus/neonate. Neonatal intensive care units (NICUs) are frequently called perinatal intensive care centers, although this label can only be given to those obstetrical wards that have a NICU. Some predominantly American obstetricians consider only the care of high-risk pregnancies/fetuses/neonates within the category of perinatology. This is unfortunate since there are multiple overlaps and pregnancies considered low-risk can turn into high-risk at any moment.

The importance of perinatal medicine is growing rapidly and is making great and varied scientific progress. Clinical innovation and research on maternal–fetal interventions have become essential for the development of perinatal medicine. Leaders in perinatal medicine should create and sustain an organizational culture of professional integrity in fetal centers, where perinatal innovation and research should be conducted.[9]

Perinatology is the discipline that deals with medical conditions during birth and in the peripartum period. In other words, perinatology combines collaborative efforts from obstetrics, neonatology, and obstetric anesthesiology, along with intensive care/therapy for caring about the life and health of the mother and the fetus/neonate. The role of obstetric anesthesiology as the third pillar of perinatology has been introduced into the definition of perinatal medicine by one of us (ZP).[10] There have been extensive developments in adult intensive care therapy, and the life expectancy of severely ill pregnant and postpartum women has also improved considerably. Therefore, clinicians of these three disciplines who care for pregnant and puerperal women, fetal patients, and neonates are perinatologists.

The old concept took the cutting of the umbilical cord as the meeting point of obstetrics and neonatology. In case of an operative delivery, the invited anesthesiologist had never seen the patient before. The common thinking and collaboration of obstetrician, neonatologist, and anesthesiologist throughout the perinatal period are crucial. For example, the decision on performing a cesarean delivery and the planning and timing of the surgery require not only an obstetrical but rather a multidisciplinary, perinatological approach. Obstetrical anesthesia and intensive care play an important role in the avoidance of maternal and fetal complications since physiological alterations involved with pregnancy as well as conditions of the fetal "well-being" have to be considered. Cesarean section has become one of the most often performed surgeries in the world,[11] and the anesthesia required for it has greatly progressed in the past decades.

Disorders requiring intensive care occur rarely during pregnancy; however, the great obstetrical syndromes, septic conditions, postoperative complications, etc., mean serious challenges for the perinatal centers.[12–15] Most common obstetrical reasons for admission are disorders involving high blood pressure and its complications as well as massive bleeding in the postpartum period. Maternal mortality has significantly decreased in developed countries due to the development of perinatology, including the development of obstetrical anesthesia and intensive care; however, prevention of such conditions and providing adequate level of care is still a serious problem for developing countries. The obstetrical conditions requiring mainly intensive care are significant factors in the maternal morbidity and mortality, and timely management of these conditions is critical in order to avoid the severe outcome.

Preeclampsia/Eclampsia/Hemolysis, Elevated Liver Enzymes, Low Platelet Count (HELLP) Syndrome

High blood pressure occurs in 10% of pregnancies, and preeclampsia occurs in 5%. Their frequency rose by 25% in the past 2 decades, and they play a significant role in premature birth. Preeclampsia is the disease of the mother, the fetus, and the placenta. It is a progressive, multisystemic maternal and fetal life-threatening condition, which is accompanied by high blood pressure and other organ dysfunction.[16] Its development can be traced back to multiple origins; it can occur at different gestational ages and in variable severity. Its precise etiology is still unknown despite excessive research.[17–21] Eclampsia is a multisystemic disease associated with various complications, which individually or in combination, can lead to maternal–fetal morbidity and mortality.

Currently, preeclampsia is classified based on the development of clinical symptoms and the severity of its course. Based on clinical classification, preeclampsia can be early onset (hypoperfusion) (less than week 34) and late-onset (hyperperfusion) (more than week 34), as well as mild and severe based on its course. Early onset preeclampsia is often accompanied by fetal growth restriction and is usually associated with severe clinical symptoms. Dysfunction of the extravillous cytotrophoblasts and, therefore, failure of transformation of the spiral arteries, and consequently, the decreased uteroplacental circulation is of particular importance in its pathophysiology.[18] This causes ischemic stress, due to which the balance of the angiogenic and antiangiogenic factors is upset, causing endothelial damage, systemic inflammatory response, and multiple organ failure. The amount of circulating blood and, therefore, the cardiac output is low, and vascular resistance is high. The outcome of the pregnancy is unfavorable for both the mother and the fetus. Termination of the pregnancy is often necessary due to threatening eclampsia or threatening intrauterine asphyxia.

In the case of late-onset preeclampsia, the effect of different chronic stress factors, such as obesity, diabetes, renal, metabolic, and autoimmune diseases, are more dominant, and the vascular and endothelial response to placental factors can also be increased. This is considered a maternal disease.

In healthy pregnancy, the vascular system is in vasodilation, which causes decreased blood pressure as well as increased heart rate and cardiac output. This can partially be explained by decreased responsiveness to angiotensin and norepinephrine (NE) and partially by increased nitrogen monoxide and prostacyclin secretion. Changes in the renin-angiotensin system and cortisol excretion cause fluid and salt retention with increased plasma volume. The hemodynamic status is different from that of normal pregnancy in both forms of preeclampsia.

Definitive therapy of preeclampsia is the termination of the pregnancy in order to prevent severe maternal and fetal complications. Its timing depends on the gestational age, the severity of the disease, as well as the condition of the mother and the fetus. "Waiting" is not an option in case of severe preeclampsia; immediate termination of the pregnancy is necessary in order to prevent the fetal–maternal complications. In case of preeclampsia occurring before gestational week 34, the mother has to be transported to a center, which is also involved in premature birth care, where 48 hours of waiting is permissible under close monitoring until waiting for the effect of steroid prophylaxis.

Hydralazine, labetalol, and nifedipine are recommended to treat severe hypertension, but these alone do not prevent eclampsia. Intravenous magnesium sulfate is necessary during pregnancy and delivery as well as in the postpartum period in order to prevent eclampsia. After a starting dose of 4–6 gm/hour, it should be continued with a maintenance dose of 1–2 gm/hour with regular monitoring of the magnesium level. In case of decreased renal function and urine output, the risk of magnesium intoxication emerges. This can be detected based on the clinical signs (patella reflex, respiratory depression, arrhythmia) and on follow-up examination every 1–2 hours as well as by checking the magnesium serum level every 6 hours. Calcium gluconate should be administered in case of magnesium intoxication. Rehydration of the patients with preeclampsia should be performed carefully; administration of significant amount of fluid should be avoided due to the risk of lung edema. It is recommended to be administered with an infusion pump at a pace of 80–100 mL/hour.

One of the most severe forms of preeclampsia is HELLP syndrome, which is associated with hemolysis, increased liver enzymes, and low platelet count, and it occurs in 0.1–1% of pregnancies. Typical clinical symptoms include epigastric pain and pain under the right side of the ribcage, often accompanied by nausea and vomiting. Hypertension and proteinuria are also present in 85% of the cases. It is usually diagnosed between weeks 28 and 36, but the symptoms can occur in the postpartum period, too. Its precise etiology is still unknown despite excessive research.[22–25] HELLP syndrome can be diagnosed by the presence of the typical laboratory alterations.[26] Microangiopathic hemolytic anemia is present in this condition; however, it occurs in many other disorders, such as thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS).[27]

Approximately 800 women die from pregnancy or childbirth-related complications around the world every day, 99% of which occur in developing countries.[28] In majority of cases, deaths are related to preeclampsia and eclampsia. Unfortunately, this alarming trend of mortality persists as 287,000 women lost their lives to pregnancy or childbirth-related causes in 2010.[28] The purpose of new adjusted and simplified International Academy of Perinatal Medicine (IAPM) guidelines is specifically lowering maternal mortality by decreasing preventable deaths in developing countries (particularly in remote rural areas) by using rather cheap medicines used to control chronic and gestational hypertension, prevent preeclampsia in high-risk pregnancies, and treat severe preeclampsia and eclampsia.[29]

Regional anesthesia is more favorable than general anesthesia in case of patients with preeclampsia. Use of spinal anesthesia has been controversial for a long time in pregnancies with preeclampsia due to the quick effect, which carries the risk of sudden drop in blood pressure. However, studies have demonstrated that the extent of blood pressure decrease, the amount of the infusions used, the necessary ephedrine doses, and the maternal and fetal outcome are similar during cesarean section performed in epidural and spinal anesthesia in this patient group.

The decision is most difficult in case of patients with thrombocytopenia. In case of thrombocytopenia, platelet count trend is more important information than the current platelet count; however, the value at which spinal or epidural anesthesia can be safely performed has not been yet determined. The limit is determined to be 65,000–70,000/μL.[30] Since the incidence of spinal hematoma is lower with spinal anesthesia, this should be preferred. The mother has to be closely monitored in the postpartum period after regional anesthesia performed with lower platelet count, with particular regard to neurological alterations. The possibility of spinal hematoma development should always be considered in prolonged motor and sensory block; therefore, urgent computed tomography (CT) and magnetic resonance imaging (MRI) might become necessary. The earlier (within 6–12 hours) the neurosurgical intervention, such as laminectomy, is performed, the better the prognosis, so even full recovery can be hoped for. Removal of the epidural cannula is only recommended after the resolution of bleeding abnormalities as well as thrombocytopenia (over 100,000/μL).

If a bleeding disorder can be confirmed based on the clinical and laboratory signs, then general anesthesia has to be performed, as well as in cases when the patient's cardiopulmonary condition is not stable. Decrease of the platelet count can occur dramatically over just a few hours,

so the decision must always be made based on recent reports (within 1–2 hours).

The anesthesiologist has to face more challenges during general anesthesia. One of the risk factors is the difficult intubation or risk of aspiration due to failed intubation. Drug interactions and increased systemic response due to preeclampsia also have to be taken into consideration during intubation. Hypertensive crisis can lead to stroke. Antihypertensive agents (e.g., labetalol), short-acting opioids (e.g., remifentanil), and magnesium sulfate should be administered during induction. Failed intubation is significantly more common among obstetrical patients compared to general surgical patients (1/280 vs 1/2230).[31] This is especially true for pregnancies with preeclampsia due to the associated edema and vulnerability of the mucous membrane. The Mallampati classification not only changes during pregnancy, but it can become worse during the few hours of labor.

Invasive hemodynamic monitoring techniques might also become necessary in case of severe preeclampsia. Invasive arterial blood pressure measurement helps ensure frequent blood sampling in order to check the acid-base and respiratory status as well as to perform liver function and other laboratory tests. Central venous catheter monitoring is similarly often needed; however, catheterization of the pulmonary artery is only used occasionally. Echocardiography is recommended in severe cases, primarily in order to timely recognize peripartum cardiomyopathy.

Peripartum Hemorrhage

Obstetrical bleeding is the leading factor of maternal mortality in developing countries and peripartum morbidity in developed countries. It occurs in 5% of pregnancies. One reason for insufficient care is the fact that actual recognition of the severity of hemorrhage is almost always delayed since physiological changes associated with pregnancy make the diagnosis difficult, and the treatment team underestimates its extent in many cases. Lack of local protocols and often inappropriate communication of the co-specialties make the appropriate treatment even more difficult. Due to the above, the well-organized cooperation of the team participating in the care of pregnant women is challenging.[32]

It is known from the physiology of pregnancy that pregnancy is a procoagulant condition, which reaches its maximum by the time of delivery, and the level of the procoagulant factors increases except for factor XI. Factor VII increases in the highest degree, up to 10-fold, while the plasma level of factors II, V, VIII, X, and XII shows slight elevation. Von Willebrand factor and fibrinogen levels double by the end of the third trimester, so the fibrinogen level at the time of delivery is 4–6 gm/L, and the fibrinolytic activity decreases. Benign gestational thrombocytopenia (<150,000/μL) occurs in 6–15% of pregnancies. The above changes result in shorter prothrombin time (PT) and activated partial thromboplastin time (aPTT) than the laboratory normal values in case of static coagulation tests, and the bedside, dynamic, so-called viscoelastic tests (thromboelastometry or thromboelastography) also confirm increased coagulation.

Besides the procoagulant condition, the plasma volume reaches its maximum by the time of delivery, preparing the mother for the blood loss associated with the delivery; therefore, typical clinical symptoms of hypovolemia might not be present in case of relatively significant blood loss due to physiological hemodilution. Due to the above, the standard coagulation tests show normal values (PT/aPTT) even after relatively significant blood loss during massive obstetrical bleeding. Severe peripartum hemorrhage is defined as blood loss exceeding 1500 mL.

The development, type, and severity of the bleeding disorder depend on the etiology of the bleeding. Atony of the uterus and damage to the birth canal rarely leads to a bleeding disorder, even in case of significant blood loss. Currently, it is evident that decrease in the fibrinogen level (value below 3 gm/L, but especially below 2 gm/L) is an important prognostic factor for the worsening of the peripartum bleeding. Evaluable data can be obtained with viscoelastic tests in the first 7–10 minutes, making the necessary therapeutic decision much faster. The ClotPro fibrinogen (FIB)—test and rotational thromboelastometry (ROTEM) FIBTEM analysis can be used to accurately monitor the need for correction of fibrinogen levels. Therefore, the point-of-care tests help determine in time whether the bleeding is caused by a bleeding disorder or it "only" has obstetrical cause.

Adequate treatment of massive obstetrical bleeding requires proper coordination of several specialties. This means that the obstetrician, the anesthesiologist, the transfusion specialist, and the laboratory diagnostic specialist work together parallelly with continuous consultation, ideally according to a previously determined and practiced policy (protocol).

The task of the anesthesiologist in case of occurrence of bleeding is the hemodynamic stabilization of the patient, initiation of volume replacement, as well as administration of blood and factor products in every case. In parallel, the obstetrician tries to find the cause of bleeding and treat it surgically. This should always be started with manual exploration of the uterine cavity in order to rule out the possible injury. Hemostasis can be supplemented by tamponade (balloon catheter tamponade). Since atony is the most common cause of massive obstetrical bleeding, uterotonic drugs must also be administered immediately. Prophylactic administration of oxytocin is standard procedure in order to prevent postpartum bleeding; however, oxytocin can have several serious side effects—hypotension, tachycardia, and ST depression. Intravenous 5 NE is the most common prophylactic dose after cutting the umbilical cord. If it is insufficient, the dose can be increased up to 40 NE. It is important to initiate prostaglandin products [misoprostol: prostaglandin E_2 (PGE2), sulprostone: Nalador] in time, but their side effects also have to be known (hypertension,

bronchospasm). If these measures fail, invasive interventions must be performed. In many cases, hysterectomy can be avoided by ligature of the hypogastric artery, but it is not rare that the mother's life can only be saved with hysterectomy.[33–36]

Besides surgical treatment, anesthesia has to try to maintain the target values important for coagulation (pH >7.2, Ca >1 mmol/L, T >35°C, hemoglobin >80–100 gm/L) as well as appropriate blood pressure. These are the foundations of the stable hemostasis. Treatment of massive obstetrical bleeding can only be successful by maintaining the above parameters. Red blood cell transfusions must be initiated immediately, and hemoglobin level must be kept over 80 gm/L. Additional products may be required:

- Tranexamic acid: Several obstetrical studies have confirmed that progression of bleeding can be prevented by the inhibition of hyperfibrinolysis occurring due to coagulation taking place on the large wound surface of the uterus. It should be routinely administered in case of atonic bleeding per the guidelines. Before the administration of fibrinogen concentrate, 2 gm tranexamic acid should be given to the patient.
- Fibrinogen concentrate: Fibrinogen concentrate is given in order to correct hypofibrinogenemia. Its use is easy, it is available in powder form, and it can be administered immediately after dissolution—a 60 mg/kg body weight dose increases fibrinogen level by 1 gm/L. A target value of 2–3 gm/L must be achieved during the treatment of massive obstetrical bleeding. About 2 gm tranexamic acid and 2–4 gm fibrinogen as well as further fibrinogen and prothrombin complex must always be available in the delivery room.
- Thrombocyte concentrate: Platelet count must be maintained above 50 gm/L for successful treatment in case of massive obstetrical bleeding. Therefore, if the platelet count falls under 75 gm/L, thrombocyte suspension should be requested. Quick decrease of the platelet count should only be anticipated in cases that cause disseminated intravascular coagulation (DIC) (amniotic fluid embolism, placental abruption, severe preeclampsia/HELLP syndrome).
- Prothrombin complex concentrate (PCC): Four-factor PCC.
- Recombined VIIa (rFVIIa) factor: Effects—intensive thrombin generation, strong thrombocyte activation, stable coagulum formation, and increase of the thrombocyte function. Its administration is necessary in severe postpartum bleeding, if the uterus is empty, and any type of lesion can be excluded if uterotonic drugs and other therapeutical interventions are insufficient at stopping the bleeding. Its early administration may eliminate the need for invasive surgical interventions, including hysterectomy. Before the administration of rFVIIa, it should be ensured that the fibrinogen level is >1.5–2 gm/L, the platelet count is at least 50 gm/L, and relevant elements of hemostasis have to be managed (arterial pH >7.2, core temperate >35°C, ionized Ca^{2+} >0.9 mmol/L). Quick changes in the coagulation system must be monitored by viscoelastic POCTs.

Conclusion

There currently is no effective means for the prevention of preeclampsia. Preeclampsia increases the risk of patients developing hypertension later in life.[37] Improvements in the diagnosis of preeclampsia may lead to better outcomes for both the mothers and the fetal/neonatal patients. Peripartum critical care requires a multidisciplinary team approach, with many preeclamptic women receiving neuraxial analgesia or anesthesia.[38] Women with severe preeclampsia may require special intensive care, and this should meet the same standards afforded to other acutely unwell patients.

Treatment of severe peripartum hemorrhage is also a typical teamwork in perinatology. During modern treatment of secondary coagulopathy associated with massive postpartum bleeding, therapy should be based on stable factor concentrates and should be target-oriented and monitored by viscoelastic tests. The local policy has to be developed based on current professional requirements, having regard to the local conditions (it must be clear who does what, when; where certain things can be found, etc.), and compliance has to be ensured by regular training, providing the sources, and audits.

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