

## Coagulopathy and obstetric anesthesia

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Coagulation disorders are a routine problem encountered by obstetric anesthesiologists. Certainly the most frequent question that they need to answer is to whether epidural anesthesia/analgesia can be performed in a particular patient without risking that a neuraxial hematoma occurs with its own devastating consequences. This question arises both in normal pregnant patients in whom the fear of ignoring an inherited or acquired but asymptomatic coagulation disorder is always present but also in patients with pregnancy-related disease and particularly in patients with pre-eclampsia. This short review will also discuss recent addition to our knowledge regarding obstetric disseminated intravascular coagulation (DIC) which often accompanies hemorrhage and increases its severity.

### EPIDURAL ANESTHESIA AND COAGULATION DISORDERS

This question underlies three problems: firstly, should biological tests be performed before any neuraxial block even in normal patients? Secondly if tests are performed, which are sensitive and specific enough to uncover patients at risk? Finally if tests are performed, what are the adequate thresholds below which the risk of hematoma is increased?

There are unfortunately very few scientific answers to these questions. Strategies accepted for non pregnant surgical patients may not necessarily apply to pregnant patients. In his classic review on preoperative testing Rapaport stated that "when the whole blood clotting time and the Duke bleeding time were the tests used to screen hemostatic function preoperatively, the question: Preoperative hemostatic evaluation, which tests, if any, was easy to answer: do not bother with these insensitive tests, rely on the patient's history (1). Several studies have confirmed that preoperative evaluation of hemostatic function can be adequately assessed by clinical screening in most patients. JANVIER *et al.* (2) prospectively studied 4141 patients scheduled to undergo vascular surgery and obtained a screening history, physical examination as well as biolo-

gical tests (platelet count, bleeding time [BT], prothrombin time [PT], activated partial thromboplastin time [aPTT] and fibrinogen plasma concentration). One patient had prolonged PT and 19 had prolonged aPTT (0.48%). A potential bleeding risk was found in only 8 patients: factor XI deficiency (n = 3), anti VII antibodies (n = 1), Willebrand's disease (n = 4). Three out of these 8 patients had a positive screening history and thus screening was useful in only 5/4141 (1.2 /1000). This very low incidence of underlying coagulation disorders with potential significant risk may not be found in pregnant patients. There are very few studies available which have examined that question. CHOQUET *et al.* reported in an abstract that they had performed pre-anesthetic evaluation and blood coagulation studies in 2219 pregnant patients during a 10 month period (3). 46 (18 /1000) had coagulation abnormalities of which 6 (3 /1000) were discovered only by biological testing: immune thrombocytopenic purpura (1 patient), gestational thrombocytopenia (4 patients) and factor V deficiency (1 patient). Although the incidence of underlying coagulation disorders is greater than in studies of surgical patients (3 vs 1 /1000, see above), it is difficult to conclude because the clinical profile of these patients and their disease severity were not described. However, because none of these patients had epidural analgesia performed, it is likely that biological abnormalities discovered were severe enough to discourage from undertaking an invasive procedure. Apart from medicolegal issues which are poor value in this debate, proponents of biological testing in pregnant patients suggest several more acceptable arguments: patients may protect against the doctor who fails to take an adequate history, some patients may give an unreliable history or patients in labor pain may be more unreliable than others. Maybe more significant is the fact that the abnormality that causes bleeding

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may become apparent only after surgery/ dental extractions/ delivery and many patients have not yet encountered those situations before because of their young age (factor XI deficiency, Willebrand). Finally, acquired hemostatic defects (i.e. thrombocytopenia) can be related to pregnancy. Von Willebrand disease is such a disease where patients can long remain asymptomatic. KADIR *et al.* showed that in a cohort of patients with Von Willebrand's disease, diagnosis of a bleeding disorder was not known in 11/31 patients. Diagnosis was made in 2 women following post-abortal or post-partum bleeding complications (4). It is also a complex disease in which the underlying biological abnormality varies from quantitative to qualitative with several subtypes. In Von Willebrand's disease type I and 2N for example, aPTT is corrected in the majority of patients at the time of delivery due to pregnancy-related increases in clotting factors (including von Willebrand antigen). As most factors are increased at supranormal values, performing aPTT and PT before an epidural is generally useless. By contrast, we believe that assessment of coagulation in early pregnancy is useful because it can detect inherited or acquired (before pregnancy) disease which follow-up during pregnancy may be useful. Epidural anesthesia is said to be safe when the level of von Willebrand antigen is greater than 50 U/dl (either spontaneously or after desmopressin administration) and there are only very rare cases described in the literature to support that motion (5).

Practices vary widely between countries. In a French study, SIMON *et al.* showed that almost every French anesthesiologist questioned asks for platelet count being performed before deciding whether the epidural anesthesia can be done or not (6). Moreover, the "safe" platelet count in normal patients is believed to be at 100 000/mm<sup>3</sup> for more than 50% of these anesthesiologists. It is of note that only 14% would perform a neuraxial block when the platelet count is below 80 000/mm<sup>3</sup>. by contrast, a recent study has shown that more than two-third of anesthesiologists from the UK would puncture with a platelet count below 80 000/mm<sup>3</sup> (7). These latter practices are supported by reviews written by experts (8). Although it is difficult to decide whether the liberal or conservative approach is the most adequate, this question is likely to be of little relevance in the clinical scene because the incidence of gestational thrombocytopenia with platelet count less than 80 000/mm<sup>3</sup> is less than 1% of pregnancies according to BURROWS *et al.* (9) and does not explain why national rates of

epidural anesthesia vary from 20 to 60% in these two countries.

Drug-induced coagulation changes are also often seen in patients. Unfractionated heparin (UFH) or low molecular weight heparins (LMWH) are more and more often used based on the perception that thromboembolic complications are now a leading cause of maternal mortality and that these drugs have the potential to protect against this risk. However, one should bear in mind that pregnancy can modify the pharmacokinetics of these drugs and thus may require more often biologic monitoring to adapt doses. ANDERSON *et al.* reported on ten patients in a 2-yr period who had term pregnancy and who were receiving subcutaneous heparin twice a day for prevention/treatment of thromboembolic disease. aPTT was maintained at twice the normal value during treatment (i.e. heparin blood concentration was between 0.2 - 0.4 U.mL<sup>-1</sup>) (10). The interval between the last dose and delivery was 14-39 hours and aPTT remained abnormal in 5 cases. Thus only five women had epidural analgesia. Protamin was administered in 3 cases and significant hemorrhage was reported in one patient. By contrast, in the early part of the third trimester, heparin resistance is the rule. BRANCAZIO *et al.* demonstrated that aPTT changes following a similar dose of UFH were much more modest than in non pregnant women (11). Pharmacokinetics of UFH is thus variably modified according to the term of pregnancy and this requires precise adaptation with frequent aPTT monitoring. LMWH administration also can lead to catastrophic neuraxial hematoma as demonstrated by the recent US epidemic seen after the wide introduction of enoxaparin in orthopedic patients (12). This explains why HORLOCKER and WEDEL have tried to produce guidelines on how to safely use LMWH (13). These guidelines can be summarized as follows :

- the smallest effective dose of LMWH should be administered perioperatively
- LMWH therapy should be delayed postoperatively as long as possible (a minimum of 12h and ideally 24h postoperatively)
- antiplatelet or oral anticoagulant medications administered in combination with LMWH may increase the risk.
- the risk of spinal hematoma in patients with indwelling catheters is almost certainly increased
- removal of the catheter should occur when anti-coagulant activity is low. Skipping the evening dose of LMWH should always be considered.

These guidelines can certainly be applied to pregnant women at the time of delivery although changes in the pharmacokinetics of enoxaparin may slightly modify the strategy. In third trimester patients treated with enoxaparin, CASELE *et al.* have shown that peak and duration of antiXa activity were significantly less than in non pregnant patients (Changes in the pharmacokinetics of enoxaparin sodium during pregnancy) (14). This can be explained by the increased body weight and the increased glomerular filtration rate of pregnant patients. Whereas aPTT is of great help to monitor UFH activity, the place of antiXa activity to monitor LMWH therapy in pregnant patients is difficult to define and the two, options (fixed or adapted dose) are possible (15). However, because duration and activity of LMWH are decreased in term pregnant women, guidelines proposed in non pregnant patients are thus more stringent and should be used safely in pregnant women.

Aspirin decreases the rate of occurrence of preeclampsia by about 15% and its efficacy is probably better in high risk groups and with doses > 75 mg daily (16). From studies in which pregnant or non pregnant patients receiving aspirin also received safely epidural analgesia (17, 18, 19), it has been stated that neuraxial blocks pose no risk when performed in patients receiving aspirin. However, the methodology of these studies suggests that the conclusions are not as clear as it seems at first glance. SIBAI *et al.* published a secondary analysis of their data supporting the fact that epidural block is safe because no complication occurred in patients treated by aspirin (20). This study has however a number of limitations. The number of women receiving aspirin was insufficient to ensure safety regarding a rae event (n = 451), the study randomization was done for aspirin and not for epidural administration. Moreover, the data were known for only 52% of women (1629/3135) and women were treated in 7 centers with epidural rates ranging from 27 to 94%. Most importantly, anesthesiologists were aware of the result of the BT before deciding to perform (or not) the epidural block and this translated into the fact that women receiving an epidural had shorter BT. This is of course not to suggest that BT should be performed before epidural or spinal anesthesia in patients using aspirin because BT is not correlated with the risk of hemorrhage (21). BT is however a marker of aspirin-platelet combination and is a witness of anti-platelet activity. The recent French expert conference has summarized its recommendations regarding the use of neuraxial blocks in

patients receiving aspirin. Regional anesthesia can be performed if the time interval between the last dose and the neuraxial block is > 2 days (22) and if a significant risk associated with general anesthesia (which is almost always true in pregnant patients). Single shot spinal anesthesia should be preferred and repeated postoperative/postpartum surveillance is mandatory. In other cases, decision should be tailored to each patient and whenever possible after discussion between physicians. When doubt remains, the principle of precaution should prevail.

Preclampsia is also of concern because coagulopathy can occur and general anesthesia carries by itself special risks in this population (facial edema and difficult intubation, hypertensive crisis...). Several workers have shown that spinal anesthesia does not worsen hemodynamics more than epidural does (23) and is now recommended as the technique of choice in many institutions. However, the threshold of platelet count at which neuraxial block becomes contra-indicated is unclear. HOOD *et al.* (23) did not make any statement whereas WALLACE *et al.* (24) stated that "women with platelet count < 100.000/mm<sup>3</sup> excluded". LUCAS M. J. *et al.* (25) said they placed "no restriction on the severity of thrombocytopenia" while SHARWOOD-SMITH *et al.* (26) and RAMANATHAN J. *et al.* (27) "excluded patients if coagulopathy was present" but did not define more precisely what they meant by coagulopathy. Finally in the recent study by HEAD B. B. *et al.* (28), "patients were excluded if platelets < 80 000/mm<sup>3</sup>". Although these differences indicate that a consensus has to be reached as far as the platelet count is concerned, it is interesting to note that most studies place their threshold between 80 and 100 000 /mm<sup>3</sup>. A recent study has shown that corticosteroids administered for fetal reasons maintain the platelet count above 80 000/mm<sup>3</sup> in most preeclamptics and this has increased the number of women in whom epidural blocks could be performed (29).

#### OBSTETRIC DIC AND ANESTHESIA

Hemorrhage is a leading cause of maternal death in several countries and is often associated with DIC. A recent study has shown that concentrations of tissue factor (TF) and its inhibitor (tissue factor pathway inhibitor [TFPI]) are much greater in «obstetric tissues» (i.e. placenta and myometrium) than in other tissues or than in non pregnant patients (30). As TF activates the coagulation pathway and combining with factor VII, this explains why DIC is more often seen in pregnant patients.

The anesthesiologist role in patients with DIC is at least twofold : firstly, symptomatic treatment aimed at maintaining oxygen delivery to tissues should be started (transfusion of red cells, oxygen administration/mechanical ventilation  $\pm$  inotropic support) as well as antibiotic therapy because underlying infection is frequent. Treatment of DIC itself is much more controversial. Administration of fresh frozen plasma (FFP) has long been blamed to give "fuel to the fire" but is nowadays a mainstay of therapy (31) when the cause of bleeding cannot be rapidly stopped by prostaglandins, uterine artery ligation or embolisation. With more aggressive and earlier treatment of the cause, a reduced number of patients will require blood products. The pharmacologic approach of DIC is still under investigation. Antithrombin has been studied in patients with septic shock and has been shown to marginally improve survival rate in this population (31). Indeed, antithrombin decreases mortality rate but in a non significant manner although it decreases organ failure rate and decreases the duration of DIC. There are no good studies of antithrombin administration in pregnant patients. Recently, activated factor VII (Novoseven®) has been successfully used in several bleeding situations including one case report of obstetric bleeding (32). Although it is of course too early to advocate the use of FVIIa in this situation, studies should be performed because preliminary data are encouraging.

## CONCLUSION

The obstetric anesthesiologist is surrounded by many patients in whom coagulopathy is present or who are at risk of coagulopathy. Decisions are often based on opinions rather than on facts and liberal or more conservative approaches are difficult to challenge. Studies are urgently needed to improve our knowledge of coagulation in pregnant women.

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