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Procalcitonin; a feasible biomarker for severe bacterial infections in Obstetrics and Gynecology?

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Peripartum sepsis is still a concern in Obstetrics and Gynecology in 2018. Sepsis is associated with significant morbidity in obstetric population and is one of the major causes of maternal mortality (1). Although universally agreed definition for maternal sepsis is lacking, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection (2).

Timely diagnosis and early initiation with intravenous antibiotic treatment are the key elements for successful management of severe infections. The mortality associated with sepsis is >10% and septic shock >30%. This is also the case in Obstetrics and Gynecology. It is thought that half of the fatal cases of puerperal sepsis can be prevented with early detection of septic condition (1).

The rate of serious sepsis is 1.8 per 1000 pregnant women in Europe (3). In a recently reported study 17% of sepsis were diagnosed antepartum, 36% intrapartum and 47% were diagnosed in the postpartum period (3). The source of infection was most often the genital tract (61%), followed by the urinary tract in 25% of cases (3). Maternal sepsis was also a risk for the fetus, as it was associated with an increased risk of preterm delivery (OR 2.8), and a high perinatal mortality rate (OR 5.8) (3).

Another US study indicates that the incidence of postoperative sepsis is increasing and up to 1% may develop septic symptoms after elective surgery (4). Infective complications are associated with common operations, after hysterectomy surgical site infection rate is 2%, more severe deep or organ space surgical site infection account up to 1%. Risk factors for severe infectious complications include high BMI, advanced age and smoking. However, in one study with hysterectomy, deep surgical site infections were associated with younger age, longer surgical times, gynecological cancer and open hysterectomy (5). Post-operative peritonitis is a life-threatening intra-abdominal infection with high rates of mortality (5). The diagnosis of an intra-abdominal infection is primarily based on clinical assessment and high suspicion. The symptoms of sepsis may be nonspecific in young and previously healthy patients. However, the patient is typically admitted to the emergency department with abdominal pain and a systemic inflammatory response, including fever/hypothermia, tachycardia, and tachypnea. Abdominal rigidity suggests the presence of peritonitis. Signs of hypotension and hypo-perfusion such as oliguria, acute alteration of mental status and lactic acidosis are indicative of ongoing sepsis. Diagnostic imaging is often insufficient in the early stage.

Traditional biomarkers C-reactive protein (CRP) and white cell count can be used for the diagnosis of bacterial infection and antibiotic treatment monitoring, but they seem to be moderately outperformed by a more recently introduced biomarker procalcitonin (PCT). The latent period of approximately 6 h of CRP is significantly slower than that for PCT. CRP is non-specific in diagnosis of sepsis, but has a high negative predictive value. Leucocyte count is increased during pregnancy, which limits its use as infection/inflammation biomarker. More accurate biomarkers are welcome.

Procalcitonin is a serum pro-hormone that increases during body response to tissue injury, systemic inflammation and particularly, in the presence of severe bacterial infection. PCT is released from various tissues as a response to endotoxins and pro-inflammatory mediators. As PCT concentration in the blood increases significantly within the first hours in severe bacterial infections (latent period of 2–4 h), it can be used for the differential diagnosis of conditions requiring early antibiotic treatment. PCT measurements are also used for the follow-up of the treatment response as its concentration in blood decreases relatively quickly as the infection resolves (PCT plasma half-life is around 25 h) (6).

Procalcitonin is more sensitive and specific for bacterial infection while CRP is a more universal marker of any inflammation (6). In the early phase of an extensive bacterial infection, and reflecting variable microbial etiology, PCT and CRP values may not behave analogously. PCT could be an especially useful biomarker in gram-negative infections as the rise of PCT is often more significant than that in gram-positive bloodstream infections. Gram-negative *E. Coli* is the most common pathogen in blood cultures in severe obstetric infections (3).

Quantitative estimation of PCT is useful. Systemic infection (sepsis) is unlikely with PCT level of <0.5 μg/L (7). A level of 0.5–2.0 μg/L indicates possible systemic sepsis, 2.0–10.0 μg/L suggests that systemic infection (sepsis) likely and PCT levels of >10.0 μg/L indicate severe bacterial infection, almost always bacterial sepsis or septic shock. Studies have also indicated that the change in PCT values (delta-PCT)

might be more useful for diagnosing infection than single PCT measurements.

The use of PCT has been evaluated for the decision to stop antibiotic treatment. A recent meta-analysis confirms that PCT can be a feasible biomarker for the reduction of consumption and duration of antibiotics for septic patients (7). This has also been shown in newborns with early-onset sepsis (8). One of the strengths of using PCT is that it seems to be a useful tool to guide and monitor antibiotic therapy. A decrease of PCT ≥80% from peak value, or PCT ≤0.5 μg/L are commonly used criteria for stopping antibiotics (7). However, data in non-pregnant women should be extrapolated with caution to pregnant women and further prospective data are needed. A retrospective analysis indicated that the sensitivity and specificity of PCT is superior to CRP for the diagnosis of intrauterine infections in pregnant women with pre-labor rupture of membranes (9).

In newborns PCT seems to have predictive value for detection of neonatal sepsis. In a recent Norwegian study PCT was superior to CRP, white blood cell count and platelet count (10). High predictive value of PCT for early onset neonatal sepsis was found in another study. High maternal PCT predicted neonatal sepsis with >85% sensitivity, 87% specificity, 85% positive predictive value and 87% negative predictive value (11). However, reference values for PCT in pregnancy have not been established and PCT levels should always be considered on an individual patient level, taking in account the clinical condition of the patient.

In Finnish national Current Guideline for sepsis endorse the use of PCT in clinical practice to diagnose and monitor the treatment response in septic patients. A recent nationwide survey from Finland shows that the adherence to this guideline is variable and that use of PCT has not been established. The tertiary-care hospital that had highest number of PCT measurements in Finland in 2014 and 2015 used PCT mostly for monitoring antibiotic treatment. Hospitals with modest use of PCT, used it most often for diagnostics.

In conclusion, PCT seems to be a useful biomarker for severe bacterial infections and this is likely to be the case also in Obstetrics and Gynecology. PCT can also be used in the guidance of antibiotic therapy. Optimising antibiotic therapy is important on an individual-patient level but can also minimise emergence of antibiotic resistance. More data are needed to support the use of PCT in Obstetrics and Gynecology. A recent Cochrane Review concluded that the available evidence is moderate quality, with insufficient sample power per outcome. This review does not support the use of PCT-guided antimicrobial therapy of patients with septic conditions (12). Maternal sepsis rate is increasing (3) and severe infection is a significant gynecological complication. Traditional inflammation markers such as CRP and white blood cell count may be more familiar to many. However, new, more sensitive and specific biomarkers such as PCT may be more useful for the diagnosis and monitoring of patients with gynecologic operations and postpartum infections.

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