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REVIEW ARTICLE

Cytokines in the perinatal period – Part I

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ABSTRACT
Successful pregnancy requires a state of immune homeostasis. Maternal tolerance of the genetically distinct fetoplacental unit is in part mediated by maternal and fetal pro- and anti-inflammatory cytokines; these cytokines have also been implicated in different pregnancy-related pathologic states. This two-part series seeks to provide anesthesiologists with an overview on selected perinatal cytokines in an effort to identify opportunities for research and improvements in clinical care. In part one, we review basic and pregnancy-related elements of the immune system, with an emphasis on the role of cytokines. From this foundation, we offer a perspective of a unique phenomenon witnessed within obstetric anesthesia – maternal temperature elevation associated with labor epidural analgesia.

Introduction

In the half century since Sir Peter Brian Medawar and Sir Frank Macfarlane Burnet received the Nobel Prize for their work on acquired immunological tolerance,[1] an improved understanding of maternal tolerance to the genetically distinct fetoplacental unit has developed. Medawar's proposed maternal immune *suppressed* state[2] has evolved to an immune *modulated* state;[3] instead of a silenced system that allows greater susceptibility to infectious diseases, the maternal immune system retains an adaptive, robust response with distinct and overlapping mechanisms.[4] These mechanisms involve regulatory T cell (Treg) recruitment,[5,6] major histoco mpatibility complex down-regulation,[7] dendritic cell entrapment,[8] complement modulation,[9,10] chemokine silencing,[11] indolamine 2,3-dioxygenase-expressing myeloid suppressor cell production,[12] progesterone secretion,[13] and interleukin-10 (IL-10) expression.[14] Although an in-depth discussion of each mechanism is beyond the scope of this review, a partial analysis of their integration is helpful in understanding their roles.

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Cytokines: hormones of the hematopoietic system

Cytokines are a complex, pleiotropic group of soluble, cell-signaling proteins that affect the biologic behaviors of hematopoietic cells and processes, such as inflammation, septic shock and wound healing.[15] Cytokines include chemokines (direct immune cells via chemotaxis to sites of inflammation), interferons (mediate cellular responses predominately to viral infections), interleukins (promote cell proliferation, maturation, migration, differentiation, and activation) or colony-stimulating factors (stimulate proliferation and differentiation of other target cells) (Fig. 1). The term interleukin (IL) was coined in an attempt to standardize the nomenclature of molecules secreted by leukocytes. However, because a diverse number of hematopoietic and non-hematopoietic cells can produce the same interleukin, a number of redundant classification systems have been created, including a recent, novel one that uses enhanced crystallography techniques to identify distinguishing structural features.[16]

Although similar to hormones in their ability to act at systemic and local levels, cytokines are somewhat unique in the large numbers of 'target cells' responsive to their influence. Moreover, instead of production being restricted to a single organ, cytokines are

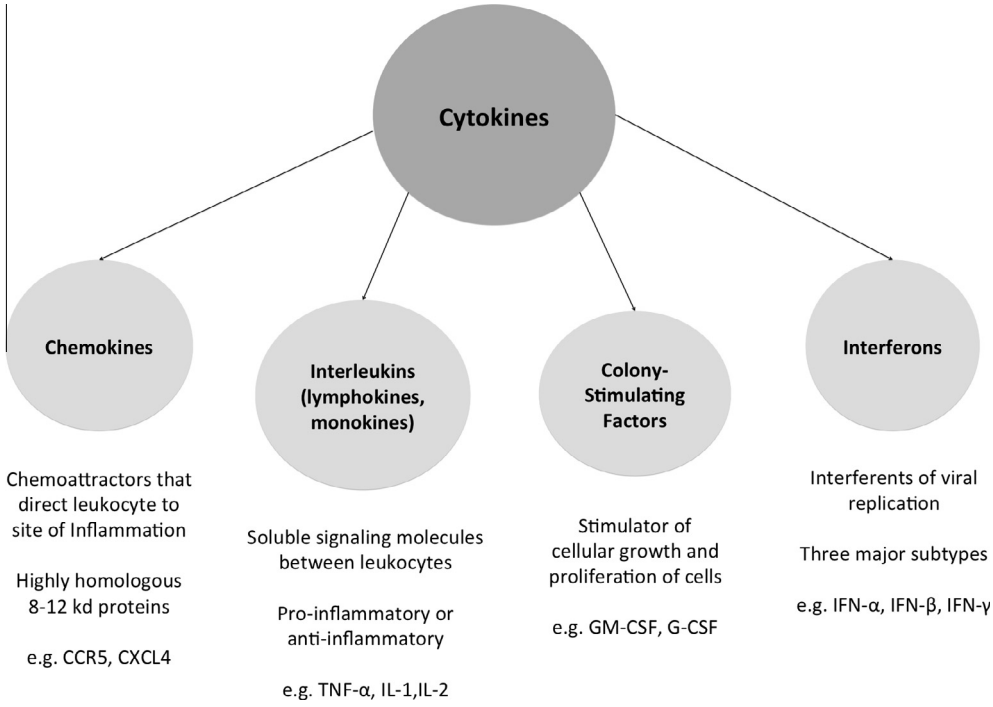

Fig. 1 An umbrella term that refers to a small soluble protein made by one cell to act upon another, cytokines have both classic and modern designations, making their nomenclature complex. For example, some cytokines have multiple names, such as the chemotactic cytokine CXCL8, which is also known as IL-8.

synthesized by a variety of hematopoietic cells, including erythroid progenitors, megakaryocytes, myeloid cells (e.g. macrophages, dendritic cells, neutrophils, mast cells), and lymphoid cells (e.g. T cells, B cells, natural killer (NK) cells).[17] Different immune cells can secrete the same cytokine and clusters of immune cells can establish intricate microenvironments that are functionally pro- or anti-inflammatory, based on the specific cytokines present.

Cell mediators of the maternal–fetal interface

In early pregnancy, as well as during the secretory phase of the menstrual cycle, the endometrium undergoes cell differentiation to facilitate implantation of the conceptus. Differentiated endometrial stromal tissue, called the decidua, represents the maternal–fetal interface where immune homeostasis and tolerance occur. The decidua is comprised of a number of maternally-derived cell types, whose specific roles are still under investigation (Fig. 2); these cells, and their relative proportions, include: decidual natural killer (dNK) cells (70%), macrophages (20%), T cells (10–20%), and rare dendritic cells, B cells and NKT cells.[18]

The dNK cells, derived from uterine NK cells, first appear in the endometrium during the secretory phase of the menstrual cycle.[18] Their primary role is to promote trophoblast invasion and vascular remodeling to maximize placental perfusion, a process likely regulated by cytokine and chemokine expression.[19] Mice deficient in NK cells demonstrate abnormally thick decidual arterioles with narrowed lumens. In the more complex spiral arteriole remodeling process present in humans, altered function of dNK cells impairs the transformation from high resistance, low-flow to low resistance, high-flow arteries; this likely has relevance to the pathogenesis of preeclampsia and fetal intrauterine growth restriction. In addition, altered dNK cell activities are associated with spontaneous pregnancy loss, and as such, have been targeted in an attempt to treat infertility and miscarriage.

In the peripheral blood, macrophages function to present antigens, remove microbes through phagocytosis, and minimize the impact of inflammatory mediators.[20] Believed to possess similar roles in the presence of placental and decidual infections, decidual macrophages may also be involved in parturition, given their selective accumulation in preterm and term patients undergoing labor when compared to those undergoing elective cesarean delivery without labor.[21] Decidual macrophages defy categorization into conventional M1 (pro-inflammatory) and M2 (anti-inflammatory) classifications given their secretion of both types of cytokines. For example, during the first trimester, decidual macrophages produce IL-10, a potent anti-inflammatory cytokine; however, with lipopolysaccharide stimula-

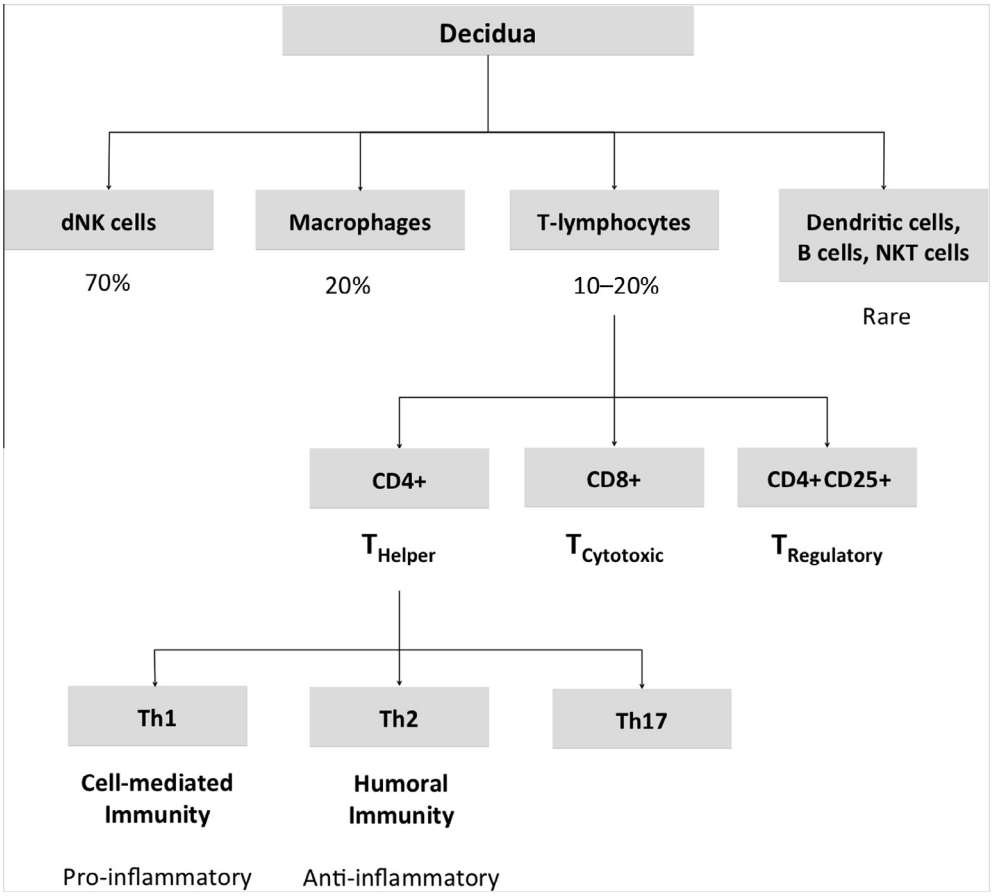

Fig. 2 Cell mediators of the maternal–fetal interface

tion, they produce pro-inflammatory cytokines such as TNF-α and IL-1β.[22]

Developed and differentiated in the thymus, T cells are lymphocytes pivotal in cell-mediated immune responses. Cell surface markers classify T cells into three subtypes: helper, cytotoxic, and regulatory.[23] CD4+ helper T (Th) cells secrete cytokines that regulate or assist in immune responses, whereas CD8+ cytotoxic T cells are directly involved in destroying cells.[23] CD4+CD25+ regulatory T cells (Treg), formerly known as suppressor T cells, are important for mitigating immune responses to infection, inflammation, autoimmunity, and cancer.[24]

The mechanisms that protect the fetoplacental unit from rejection are complex and incompletely understood, but likely involve common subsets of Th cells. Similar to the categorization of macrophages by M1/M2 phenotypes, Th1 cells are associated with the production of pro-inflammatory cytokines (e.g. IL-2, IFN-γ, TNF-α) that are responsible for cell-mediated immunity, but when present in excess, can result in widespread cytotoxic damage. In contrast, Th2 cells generally produce anti-inflammatory cytokines (e.g. IL-4, IL-5, IL-6, IL-9, IL-10, IL-13) that promote humoral immunity. The Th1/Th2 classification scheme does not adequately account for all cytokines. For example, IL-6, the strongly pro-inflammatory cytokine, is produced by the traditionally anti-inflammatory Th2 cells; moreover, IL-8, another pro-inflammatory cytokine, resists classification because it is produced by macrophages and monocytes, instead of T cells.[25,26]

Despite these issues, Wegmann et al.[27] conceptualized a successful pregnancy as involving a shift from Th1-mediated cytotoxic attacks to Th2-mediated anti-inflammatory responses to foreign fetal cells, functionally resulting in maternal immune suppression and fetal tolerance.[28] However, the similarity in observed or provoked immune responses of pregnant and non-pregnant women, such as in vaccination studies, have questioned this premise.[29]

Regardless, an ongoing pregnancy appears dependent on immunologic regulators, such as decidual Treg cells.[30–32] Destruction of Treg cells before implantation leads to early pregnancy failure.[33] In mice and humans, deleterious genetic mutations affecting Treg number or function can precipitate an aggressive systemic inflammatory response with an exaggerated release of cytokines (i.e. "cytokine storm").[34,35] During pregnancy, an increasing numbers of Treg cells are found in the maternal circulation, decidual tissues and lymph nodes,

particularly those originating from the uterus.[32,34] Ongoing human pregnancies have higher circulating levels of Treg cells than those that miscarry.[36] Rowe et al.[37] demonstrated that Treg cells selectively silence maternal immune cells that would otherwise recognize fetal-derived cells as foreign and mount an immune response; more specifically, Treg cells appear to oppose the action of Th17 cells (a subset of CD4+ T cells that produce the pro-inflammatory cytokine IL-17). As Treg cells affect the production of cytokines, cytokines in turn regulate the balance between Treg and Th1/Th2/Th17 cells during pregnancy;[34] IL-10, for example, suppresses maternal responses to the fetal allograft.[14]

Cytokine alterations in pregnancy and parturition

Maternal cytokine production is dynamic and complex throughout gestation. The process of implantation, decidual remodeling, placental development, fetal growth and parturition involve continuous modulation of cytokine balance by endogenous (e.g. estrogen or progesterone) and exogenous (e.g. preeclampsia or gestational diabetes) factors.

As indicated previously, a progressive shift from cell-mediated, pro-inflammatory, Th1 cell responses to humoral, anti-inflammatory, Th2 cell responses is initiated early in pregnancy.[38] The Th2-biased response resolves to pre-pregnant ratios by four weeks postpartum.[26] Animal studies demonstrate a dramatic increase of Th2 relative to Th1 cytokines in pregnant compared to virgin mice.[27] In humans, pro-inflammatory cytokines decrease (e.g. IL-2 and IFN-γ), and anti-inflammatory cytokines increase (e.g. IL-4 and IL-10) with ongoing pregnancies.[3,26] The Th1/Th2 paradigm also broadly summarizes the effect of sex hormones on patterns of cytokine production. During pregnancy, serum estradiol levels can increase up to 500-fold.[3] Whereas low estradiol levels generally promote Th1 responses and cell-mediated immunity, high estradiol levels promote Th2 responses and humoral immunity.[38] Progesterone exerts anti-inflammatory actions by inhibiting the production of chemokines; IL-10 levels were higher, while IL-8 and IL-1β levels were lower, in women who received progesterone compared to placebo from 24 to 34 weeks.[39] A shift towards Th2-polarity is not required for gestation, because mice genetically deficient of IL-10 and quadruple knockout mice for genes encoding four Th2 cytokines (IL-4, IL-5, IL-9 and IL-13) can sustain normal gestations.[40,41] As a consequence, it is best to consider the Th1/Th2 paradigm as a simplified representation of a complex immune system that can fail to capture subtle variations within individual cytokines.

As gestation reaches full term, an increase in pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and TNF-α) occurs in the amniotic fluid;[42,43] these pro-inflammatory cytokines participate in labor initiation and enhance cervical ripening,[43] which may represent the initial reversion back to a Th1 cytokine predominance. The levels of pro-inflammatory cytokines TNF-α, IFN-γ and IL-1β are increased in women with active labor who had vaginal compared to elective cesarean delivery.[44] Using a nonlinear mixed-effects model, Rhee at al.[45] identified that parturients with IL-1β concentrations in the highest quartile on presentation to the labor suite had a more dilated cervix, faster labor progress, and less labor pain.

Labor epidural analgesia-associated temperature elevation

Despite two decades of research, labor epidural analgesia-associated temperature elevation remains an enigma. Fusi et al.[46] and Camann et al.[47] first observed an association between the use of labor epidural analgesia and a gradual increase in maternal temperature, which typically did not result in maternal fever (>38°C). Other investigators confirmed this association,[48,49] particularly among subsets of nulliparous women at highest risk for infection and fever (e.g. prolonged rupture of membrane, higher temperature on admission, early chorioamnionitis, protracted labor and more frequent cervical examinations).[49–53] The definition of maternal fever includes ⩾37.5°C (99.5°F),[54–56] ⩾37.8°C (100°F),[50,57] and ⩾38°C (100.4°F);[51,52,54,55,58–71] ⩾38°C is most commonly used in randomized trials. The diagnosis of maternal fever can invoke a number of interventions to diagnose, prevent or treat maternal, fetal and neonatal infection or sepsis.

Although the mechanism for labor epidural analgesia-associated temperature elevation has not yet been elucidated, a number of theories have emerged, including impaired central thermoregulatory mechanisms,[46,59,71,72] imbalances between heat-producing (e.g. hyperventilation) and heat-dissipating (e.g. sweating) mechanisms due to sympathetic blockade,[46] and the antipyrexic effects of systemic opioids in patients not receiving epidural analgesia.[73] Most investigations have attributed the temperature elevation to a non-infectious, inflammatory process triggered or enabled by labor epidural analgesia.[48]

Observational studies and randomized trials have reported an incidence of maternal fever as high as 24% in the setting of epidural analgesia use.[50,52,70] Parturients experiencing fever typically have a number of risk factors, including a higher prevalence of chorioamnionitis;[49] infections within the uterus likely augment the request for labor epidural analgesia, as bacterial pathogens directly activate nociceptors[56] and may result in greater labor pain. In the absence of chorioamnionitis,

Vallejo et al.[58] observed a 1% incidence of fever in women with labor epidural analgesia.

The role of cytokines in labor epidural analgesia-associated temperature elevation

Maternal fever during labor epidural analgesia is associated with increases in maternal and cord serum inflammatory cytokines (i.e. IL-6, IL-8, IL-1β and TNF-α).[59] The cytokine IL-6 plays a role in parturition by inducing amnion and decidual cells to synthesize prostaglandins, which induces cervical ripening, but also neutrophil activation, tissue damage, and even psychological stress.[74,75] Levels of IL-6[76] are higher in patients with prolonged labor, peak immediately after delivery and normalize within 24 h.[75]

The nature of the relationship between fever and IL-6 concentrations remains obscure. As the only cytokine measured in significant amounts in the peripheral circulation,[77–79] IL-6 levels are higher during fever, with a similar pattern in the cerebrospinal fluid.[80,81] Mice genetically deficient in IL-6 fail to mount a fever response to lipopolysaccharide injection,[82] however, direct injection of IL-6 into the brain induces fever.[83–85] By contrast, the peripheral administration of high doses of IL-6 does not affect body temperature, unless injected with low doses of IL-1β.[77,83,86,87] Mice with a genetic deficiency of IL-1β fail to mount a febrile response to turpentine.[88] In-vitro[89] and in-vivo[90] studies demonstrate that IL-1 is a potent inducer of IL-6 production, suggesting that they work together to induce fever.

Peripherally circulating IL-1 and IL-6 can enter the brain via an active transport mechanism.[91,92] IL-1 induces prostaglandin production by binding to IL-1 receptor type 1 (IL-1R1), which leads to the expression of cyclooxygenase-2 (COX-2) in brain endothelial cells.[93] Similarly, Eskilsson et al.[94] observed that binding IL-6 to its α-receptor (IL-6Rα) on the brain endothelium leads to COX-2 expression and the production of inflammatory prostaglandins; however, the IL-1R1 signaling pathway was not used.[94] This indicates that peripherally released cytokines can invoke febrile responses by activating different intracellular signaling pathways.[77,94]

Following the initiation of labor epidural analgesia, Goetzl et al.[50] observed a significant increase in maternal serum IL-6 and IL-8 levels at 4 h and 8 h, but no increase in IL-1β and TNF-α. In women who subsequently became febrile, compared to those who remained afebrile, the mean baseline levels of IL-6 were not different (116.9 ± 25.0 vs. 67.4 ± 71.0 pg/mL, P=0.15).[50] Smulian et al.[95] also reported increases in IL-6 in the presence of labor epidural analgesia, with greater levels in women who developed intrapartum fever (up to 1 h postpartum). However, no differences in maternal IL-6 levels were observed in women with fever with and without clinical criteria for chorioamnionitis.[95]

In comparing the effects of intermittent (ILEA) versus continuous (CLEA) labor epidural analgesia, Mantha et al.[59] observed that the incidence of fever with ILEA was lower than in CLEA at 4 h (2/42, 4.6% versus 10/44, 22.7%, P=0.036), with no differences observed after 8 h. Significant increases in maternal serum IL-6 levels were found, with no intergroup differences up to 4 h postpartum. Neonates born to febrile versus afebrile mothers had higher temperatures (37.0 vs. 36.7°C, P=0.012), although no differences were observed in cord serum cytokines including IL-6, IL-8, IL-1β, TNF-α and granulocyte macrophage colony-stimulating factor (GM-CSF).[59] In parturients randomized to receive labor continuous spinal analgesia with sufentanil, compared to non-pharmacologic analgesic methods, Tian et al.[72] observed a significant increase in the incidence of maternal fever (24.32% vs. 5.26%, P=0.024). However, no significant differences were observed between groups in serum levels of IL-6, IL-8 and TNF-α; IL-6 and IL-8 increased in all parturients as labor progressed.

Clinical relevance, opportunities and future directions

Maternal fever during labor occurs in approximately one-third of deliveries and has significant implications for the mother and fetus.[53] Maternal temperatures >38°C have been associated with increased risks of unexplained cerebral palsy (9.3-fold increase),[96] neonatal hypoxic encephalopathy (4.7-fold increase),[97] and unexplained neonatal seizures (3.4-fold increase).[98,99] Although no evidence directly links epidural analgesia-associated fever to severe neonatal adverse outcomes, any significant temperature elevation evokes concerns for mother and neonate.

The mechanism for labor epidural analgesia associated temperature elevation is likely a non-infectious, systemic inflammation,[48,62,70] as the infection rate does not appear to be influenced.[48] Moreover, pre-treatment with antibiotics does not appear to have an effect; Sharma et al.[70] found no differences in the incidence of maternal fever in parturients receiving a prophylactic antibiotic versus placebo before initiation of labor epidural analgesia. At this time, a rapid, clinically reliable diagnostic method does not exist for distinguishing asymptomatic non-infectious from early infectious causes of maternal fever. Because cytokines have a critical role in both inflammation and infection, their maternal serum profile may assist in distinguishing the two entities; IL-6 and procalcitonin show promise as surrogate serum markers in this role.

Elevated levels of IL-6 are found in amniotic fluid, fetal cord blood and maternal serum following epidural analgesia and in the setting of chorioamnionitis; in

preterm labor and preterm premature rupture of membranes (PPROM) patients, elevated levels may also be found in vaginal secretions.[100] In term healthy parturients without PPROM who remained afebrile throughout labor and delivery, Gulati et al.[100] found a significantly lower mean serum IL-6 at admission compared to those who presented with PPROM (2.48 vs. 11.86 pg/mL, P=0.001). In the same study, women without, versus with, histological chorioamnionitis had significantly lower mean serum IL-6 level at admission (3.98 vs. 20.09 pg/mL, P<0.001). The investigators suggested admission with an IL-6 level ⩾8 pg/mL was predictive of infectious morbidity in PPROM (sensitivity 82.6%, specificity 86.3%), and all cases of maternal sepsis had IL-6 ⩾8 pg/mL (P=0.022).

Riley et al.[48] observed that a median IL-6 level >11 pg/mL at time of admission was associated with later development of fever; women in this subgroup who received epidural analgesia had an incidence of intrapartum fever significantly greater than those with admission IL-6 <11 pg/mL (36.4% vs. 15.7%, P=0.008). In women who did not receive epidural analgesia, IL-6 was not predictive of fever development. Among women who did not develop intrapartum fever, median IL-6 levels were not significantly different among those receiving, and not receiving, epidural analgesia (2.4 vs. 1.4 pg/mL, P=0.3).[48] These data suggest that underlying systemic processes may influence IL-6 levels more than the use of epidural analgesia.

Procalcitonin has been extensively studied as a biomarker for bacterial respiratory infections and sepsis.[101] In a control group of cardiac surgery patients with no evidence of infection, Aouifi et al.[102] found that mean serum procalcitonin concentrations were markedly higher in patients with septic shock (96.98 ng/mL), moderately elevated with pneumonia (4.85 ng/mL) and bacteremia (3.57 ng/mL), and remained low during mediastinitis (0.80 ng/mL); a procalcitonin threshold of 1 ng/mL was 85% sensitive and 95% specific as a marker of infection. The role of procalcitonin during pregnancy appears less useful as a diagnostic aid for infection, as the median maternal plasma concentrations of procalcitonin have been observed to be elevated in both PPROM (1.97 ng/mL) and pre-labor rupture of membranes (1.60 ng/mL).[103] Chorioamnionitis may be similar to mediastinitis, in that small increases in procalcitonin may be observed despite the presence of an infection. Future studies should examine the pattern and magnitude of changes in IL-6, procalcitonin, and other cytokines during labor and progression of maternal sepsis to determine the relationship with temperature elevation.

Methods to reduce fetal exposure to maternal inflammatory cytokines in the context of labor epidural analgesia associated fever have favorable implications to preterm infants, as elevated amniotic fluid IL-6 has been linked to an increased risk of cerebral palsy, independent of the presence of infection.[104] Specifically, in preterm infants with umbilical cord IL-6 levels >400 pg/mL, there is a six-fold increased risk of periventricular leukomalacia.[105] Unfortunately, initial efforts to mitigate the inflammatory state have been mostly ineffectively or impractical. In 2004, Goetzl et al.[106] found identical rates of fever in women randomized to receive acetaminophen or placebo in labor, with no difference in mean maximal temperature or change in temperature over time. Subsequently in 2006, Goetzl et al.[99] investigated whether systemic corticosteroids in non-diabetic parturients could attenuate or prevent fetal exposure to hyperthermia and inflammatory cytokines after epidural analgesia. The regimens consisted of intravenous low-dose methylprednisolone 25 mg every 8 h, high-dose methylprednisolone 100 mg every 4 h, or placebo. Compared to placebo, only the high-dose steroid prophylaxis was successful in decreasing the incidence of fever after labor epidural analgesia; the incidence was reduced by 90%. Moreover, the rate of neonatal sepsis evaluation was significantly lower in the high-dose compared to the low-dose group (4.1% vs. 24.0%, P<0.05), however, the incidence of asymptomatic bacteremia was increased in the high-dose group, compared to low-dose group and placebo (9.3% vs. 2.1% vs. 0%, respectively, P=0.005). A non-significant reduction in median cord blood IL-6 levels in the high-dose group (24.0 vs. 30.5 pg/mL, P=0.07) was also found.

Wang et al.[107] randomized 60 healthy term nulliparas in spontaneous labor to receive epidural analgesia alone or with epidural dexamethasone 0.2 mg/kg. In the epidural analgesia only group, a significant elevation in mean maternal temperature was observed 4 h after epidural initiation and at delivery;[107] the change in temperature had a linear relationship to maternal serum IL-6 levels. By contrast, in the group who received epidural dexamethasone, maternal temperature and IL-6 levels did not change from baseline. Limitations of the study included the relatively short total duration of labor epidural analgesia (most <5 h) and the absence of a control group who did not receive neuraxial analgesia.

Further investigations will need to identify the optimal type, timing, dose and route of corticosteroids that can diminish labor epidural analgesia-associated temperature elevation, while minimizing side effects. For example, in non-pregnant patients receiving epidural corticosteroids, a significant increase in blood glucose levels for up to seven days was observed.[108] Moreover, the potential for corticosteroids to alter cytokine balance, or mask fever and delay the diagnosis of sepsis must be evaluated. The finding that IL-6 and IL-1 act synergistically to induce the release of COX-2 enzymes and produce fever may indicate that selective inhibition of COX-2 could be a potentially viable therapeutic target to mitigate labor epidural analgesia-associated temperature elevation.

Disclosure

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