



Melatonin in Maternal Sepsis: Targeting Endothelial Dysfunction and Immune Dysregulation

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Dear Editor,

Maternal sepsis remains a leading cause of maternal mortality worldwide, despite advances in antimicrobial therapy and intensive care. Pregnancy induces unique immunological and vascular adaptations that may modify the host response to infection. Once sepsis develops, dysregulated inflammation, endothelial injury, and microcirculatory dysfunction can lead to multiple organ failure and poor maternal-fetal outcomes. These observations highlight the need for adjunctive therapies that extend beyond microbial eradication (1-4).

Melatonin (N-acetyl-5-methoxytryptamine) is increasingly recognized for pleiotropic properties beyond circadian regulation, including antioxidant, anti-inflammatory, immunomodulatory, antiapoptotic, and mitochondrial-protective effects. Although melatonin has been studied in preeclampsia and fetal growth restriction, its potential role in maternal sepsis remains underexplored (4-8). Direct evidence for melatonin in maternal sepsis is extremely limited; therefore, most inferences must be drawn from related but distinct clinical contexts.

A central event in sepsis is endothelial dysfunction. Excessive tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6) activate nuclear factor kappa-B (NF- κ B), leading to glycocalyx degradation, oxidative injury, and increased vascular permeability. In pregnancy, placental function depends on maternal vascular integrity, making endothelial preservation a key

therapeutic goal (8-10). Melatonin has been suggested to directly scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS), enhance endogenous antioxidants (superoxide dismutase, catalase, and glutathione peroxidase), suppress NF- κ B, attenuate cytokine production, preserve endothelial nitric oxide synthase (eNOS) activity, and reduce endothelial apoptosis, thereby potentially limiting organ dysfunction (5, 6, 8, 9). However, most of these findings are derived from experimental or non-pregnancy-specific studies, and their direct applicability to maternal sepsis remains to be established.

Immune dysregulation is another hallmark of sepsis. Sepsis disrupts the pregnancy-related balance between fetal tolerance and antimicrobial defense, causing excessive inflammation followed by immunosuppression. Proposed mechanisms suggest that melatonin modulates macrophage polarization, inhibits the NLR family pyrin domain containing 3 (NLRP3) inflammasome, attenuates neutrophil activation, and regulates T-cell function, potentially restoring immune homeostasis rather than indiscriminately suppressing immunity (3, 9, 10). Nevertheless, these effects have predominantly been demonstrated in models of systemic inflammation or pediatric infections, and direct evidence in maternal sepsis is currently lacking. Primary experimental studies specifically investigating these pathways in maternal sepsis models are needed to strengthen the mechanistic rationale.

Mitochondrial dysfunction contributes to sepsis-associated organ failure through impaired oxidative phosphorylation, excessive ROS production, and mitochondrial DNA damage. Based on evidence from systemic inflammation models, melatonin accumulates within mitochondria, preserves membrane potential, enhances adenosine triphosphate (ATP) production, and promotes biogenesis (8, 10-12). However, these specific mitochondrial effects of melatonin have not been directly confirmed in maternal sepsis.

The placenta synthesizes melatonin and expresses melatonin receptor type 1 (MT₁) and melatonin receptor type 2 (MT₂), suggesting endogenous roles in homeostasis. Although placental melatonin synthesis and receptor expression are established, the hypothesis that melatonin protects against infection-induced placental dysfunction in maternal sepsis remains unproven and requires further investigation (3, 5, 8, 10, 11). Evidence regarding melatonin's roles in maternal-fetal medicine further supports the biological plausibility of this hypothesis while also highlighting the absence of direct data on maternal sepsis.

Despite a strong biological rationale, clinical data on melatonin as an adjunctive therapy in maternal sepsis are very limited. Available clinical evidence from general adult sepsis, neonatal sepsis, or pediatric populations cannot be directly extrapolated to pregnant women. The studies by El Frangy et al. and others, although valuable, were conducted in neonatal populations and therefore cannot be directly translated to maternal care (7). Future research should clarify optimal dosing, pregnancy-specific pharmacokinetics, timing, and drug interactions. Well-designed randomized controlled trials are needed to determine whether mechanistic benefits translate into improved maternal and neonatal outcomes (12). No randomized controlled trials of melatonin in maternal sepsis have been conducted to date.

The most important limitation of this letter is the lack of direct evidence specifically addressing melatonin in maternal sepsis. Most of the mechanistic and clinical evidence cited herein is derived from experimental models, nonpregnant adult populations, or neonatal and pediatric studies. The pathophysiology of maternal sepsis differs in important ways from that of these populations because of pregnancy-specific immunological and vascular adaptations. Additionally, the quality and methodological rigor of the available studies vary considerably, and some are published in less widely recognized journals. Therefore, all conclusions must be interpreted with caution, and the potential role of melatonin in maternal sepsis remains hypothetical and investigational.

In conclusion, maternal sepsis involves interconnected pathways of endothelial dysfunction, immune

dysregulation, oxidative stress, and mitochondrial injury. Melatonin may simultaneously target these processes, making it a potential adjunctive candidate. Given its favorable profile in preclinical and indirect studies, further investigation is warranted. However, melatonin remains an investigational agent in maternal sepsis, and its clinical use cannot be recommended until robust, pregnancy-specific randomized clinical trials have been conducted. The title of this letter reflects its investigative and hypothesis-generating nature, and the findings should be interpreted accordingly.

Footnotes

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