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From warming skies to premature birth: environmental heat reprograms placental function

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Pregnant women face a significant risk of adverse birth outcomes when exposed to heatwaves or elevated environmental temperatures, especially during the critical windows of early and late gestation. Although the danger is clear, the biological mechanisms driving heat-induced premature birth remain poorly understood. Could maternal heat exposure reprogramme the gene expression and epigenetic architecture of the placenta—the vital organ that maintains pregnancy and supports foetal growth—thereby undermining its function? And what evidence do we really have that climate change is reshaping the physiology of the female reproductive system? In this article, we present solid evidence from human tissues and experimental models, alongside conceptual insights, to illuminate how heat stress alters placental biology in ways that can lead to preterm birth—the primary cause of neonatal and under-five childhood mortality worldwide.

Pregnancy and extreme heat: how serious are the risks?

Climate change has already driven global temperatures to rise by approximately 1.2°C above pre-industrial levels, and this trajectory is expected to continue, with potentially catastrophic consequences for human health. The frequency and intensity of heatwaves, alongside steadily increasing average temperatures, are projected to escalate sharply in the coming decades. These climatic shifts pose profound health risks, particularly for vulnerable populations with limited physiological resilience to extreme heat, including pregnant women.

During pregnancy, physiological and anatomical adaptations challenge maternal thermoregulation when exposed to excessive external heat. As pregnancy advances, internal heat production increases due to foetal and placental metabolism. However, the dissipation of this excess heat is limited by increased maternal body mass and a relative decrease in body surface area. These heat-related issues are particularly significant in women from low- and middle-income countries (LMICs), where many continue household chores and agricultural work throughout pregnancy. Population-based studies provide strong evidence that exposure to heatwaves and increasing ambient temperatures substantially raises the risk of adverse pregnancy outcomes, including preterm birth, stillbirth, and low birth weight.

Approximately 15 million babies are born preterm (before 37 weeks of gestation) worldwide each year, and over one million of these infants die due to complications associated with prematurity. The rate of preterm birth is significantly higher among women in LMICs, ranging from 10.4% in Asia to 12% in sub-Saharan Africa—almost double the rates observed in many high-income countries. This risk is further amplified by maternal exposure to heat during pregnancy.

A systematic review demonstrated a strong association between environmental temperature and preterm birth, showing an overall 5% increase in the risk of preterm birth for every 1°C rise in temperature, and a 16% increase during heatwaves. Prolonged exposure to high temperatures for over 3 months was associated with a 14% higher risk of preterm birth, whereas exposure for less than 4 weeks resulted in a 7% increase, indicating a clear dose-response relationship between heat and preterm birth. Furthermore, the World Health Organization recently reported that each 1°C rise in daily temperature above 23.9°C increases the risk of infant mortality by 22.4%. Despite these findings, the underlying biological mechanisms linking extreme heat to preterm birth remain largely unknown.

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What are the underlying mechanisms?

It is speculated that preterm birth may result from maternal heat stress caused by elevated ambient temperatures, which compromise thermoregulatory capacity, trigger cortisol release, and subsequently induce oxytocin-mediated uterine contractions and labour. A study conducted in The Gambia demonstrated that even short-term heat exposure significantly increased maternal body temperature, leading to physiological stress in both the mother and the fetus. Foetal stress, in particular, was attributed to impaired placental perfusion, arising from increased resistance in the umbilical arteries. This study offers compelling evidence that modest heat exposure can immediately alter maternal and foetal physiology. However, the effects of sustained and prolonged heat exposure on placental molecular function and how these changes may contribute to preterm birth remain to be fully elucidated.

Why does ambient temperature matter for proper placental function?

The placenta plays a crucial role in pregnancy and is essential for foetal development and growth. Foetal core temperature is approximately 0.5°C higher than maternal core temperature due to foetal metabolism. Most of this excess heat is dissipated through the placenta via a thermoregulatory mechanism that depends on maternal temperature, placental blood flow, and foetal metabolism. Prolonged exposure to elevated ambient temperatures compromises thermoregulatory capacity, thereby impairing placental function and contributing to adverse pregnancy outcomes, including preterm birth (Figure 1). A human study demonstrated that maternal exposure to 29°C in late pregnancy resulted in a reduction in average placental size compared to exposure at 20°C. Similarly, several animal studies have demonstrated that excessive heat during pregnancy significantly reduces placental weight and decreases placental transport capacity, suggesting that high temperatures adversely affect placental development and function.

Heat exposure disrupts placental gene expression and function

The current understanding of how heat exposure during pregnancy alters placental gene expression and molecular functions in humans is limited. In our recent transcriptomic study, conducted on a relatively small sample size, we observed distinct gene expression patterns in preterm

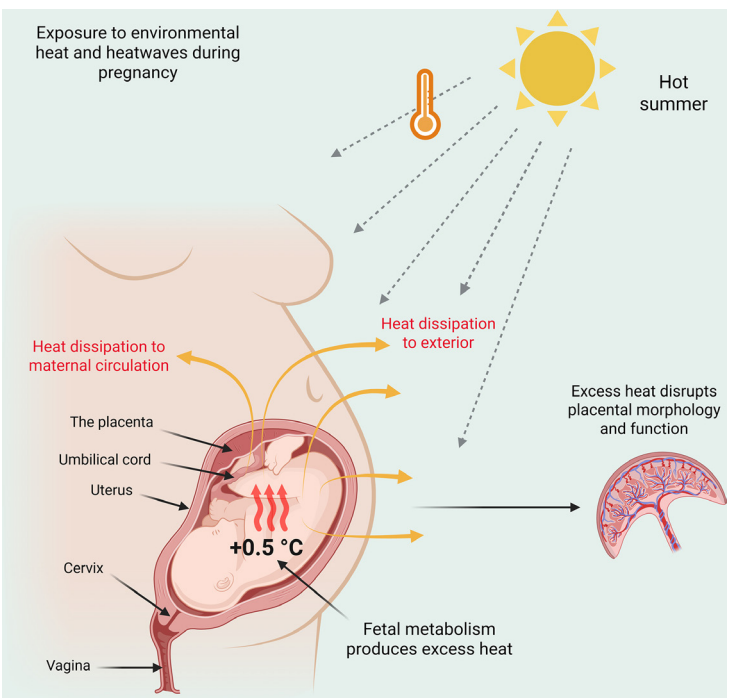


Figure 1. Foetal heat dissipation. During pregnancy, foetal body temperature is approximately 0.5°C higher than maternal core temperature due to placental and foetal metabolism. This excess heat is dissipated partly through the maternal abdominal wall to the external environment and partly into the maternal circulation via the placenta. However, when the ambient temperature is high, the rate of heat dissipation slows, leading to heat accumulation in the womb, which adversely affects placental function. This diagram was created in BioRender.com (Accessed on 3 Oct 2025).

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placentas delivered during the warmer months in the UK compared with those delivered in colder months. A total of 48 genes were differentially expressed, of which 40 were upregulated (overexpressed), the majority of which were inflammatory cytokines and chemokines in nature. These upregulated genes enriched 17 signalling pathways, including the NF-κB (nuclear factor kappa-B), IL-17 (interleukin-17), Toll-like receptor (TLR), chemokine and allograft rejection signalling pathways (Figure 2).

Under normal conditions, the placental NF-κB signalling pathway remains suppressed to sustain gestation. Its activation triggers a series of molecular events that lead to labour through the production of inflammatory cytokines, chemokines, and prostaglandin-synthesising enzymes. Premature activation of NF-κB signalling has previously been linked to preterm birth. Therefore, the increased NF-κB signalling observed in heat-exposed preterm placentas may play a role in triggering premature labour.

TLR signalling and its activation have previously been linked to spontaneous preterm birth. Stimulation of TLRs induces the release of pro-inflammatory cytokines in the placenta and foetal membranes. Additionally, activation of TLR signalling promotes uterine contractions, cervical dilation, and premature rupture of membranes. Thus, it is plausible that heat exposure during pregnancy may contribute to preterm birth by activating TLR signalling. In addition, IL-17, produced by T cells, promotes inflammation at the maternal-foetal interface of the placenta in preterm birth. Our functional enrichment analyses revealed that exposure to warmer temperatures was associated with positive enrichment of both T cell activity and IL-17 signalling in preterm placentas. This 'T cell/IL-17 signalling axis' may therefore be implicated in impaired placental function following heat exposure. Taken together, our data suggest that heat exposure may precipitate premature parturition by amplifying inflammatory and immunomodulatory signalling pathways, although this requires confirmation in larger studies (Figure 2).

An unresolved question is whether the placental molecular disruptions we observed result directly from heat effects on the placenta or are instead mediated by maternal systemic alterations induced by heat exposure during pregnancy. It is plausible that heat stress alters maternal immune balance or serum protein composition, which in turn secondarily disrupts placental function. Indeed, maternal stress following climate-related disasters, such as hurricanes, has been reported to disrupt the placental transcriptome, modulating functional pathways associated with inflammation, extracellular matrix integrity, and sensory perception.

Evidence from animal studies further reinforces this idea. A controlled study on pregnant pigs showed that maternal heat exposure during early to mid-gestation altered placental gene expression profiles. These transcriptomic changes were linked to reduced transport activity, glycoprotein production, and carbohydrate metabolism, collectively leading to placental inefficiency. Similarly, research in dairy cows has indicated that heat exposure in late gestation significantly disrupts the placental transcriptome, especially pathways involved in

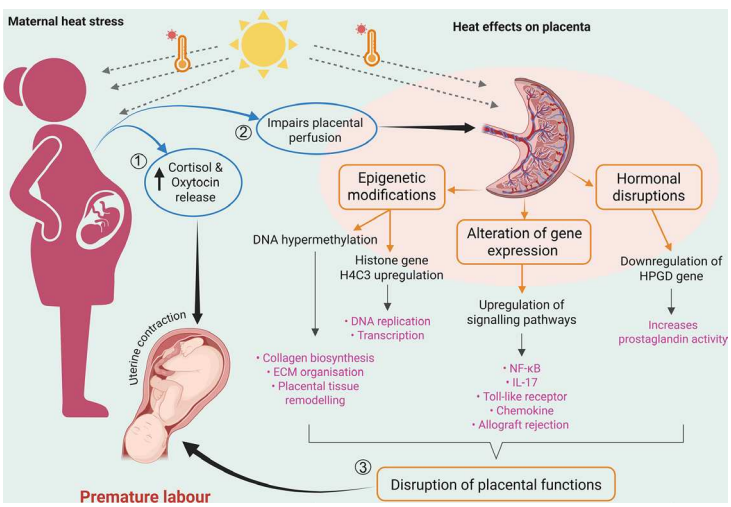


Figure 2. Alteration of maternal physiology and placental molecular functions following heat exposure during pregnancy. (1) Maternal heat stress increases systemic cortisol and oxytocin levels, which can trigger uterine contractions and labour.(2) Maternal heat stress also reduces blood flow through the umbilical artery, leading to impaired placental perfusion and foetal stress.(3) High ambient temperature causes heat to accumulate within the womb, disrupting placental function by altering gene expression, epigenetic modification, and hormone production. This diagram is created in BioRender.com (Accessed on 3 Oct 2025).

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gas and oxygen transport, nutrient transfer, inflammatory responses, and cortisol production. These changes were associated with thermoregulatory adaptations and morphological modifications in the placenta. Notably, several genes (e.g., CD5L, MMPs) and inflammation-associated signalling pathways identified in this dairy cow study were also found to be dysregulated in placentas from pregnant women who delivered during warmer months of the year.

Does heat exposure also affect the placental epigenome?

Heat stress induces epigenetic modifications, including DNA methylation and histone modifications, which help protect cells from thermal damage by adjusting the transcriptional activity of heat-responsive genes. In cattle, heat stress has been shown to cause DNA hypermethylation associated with regulatory pathways involved in collagen biosynthesis and degradation, extracellular matrix structural organisation, and placental tissue remodelling. However, very little is known about how heat exposure shapes human placental epigenetics.

In our recent study, we observed significant upregulation of the core histone gene H4C3 in preterm placentas delivered during the warmer months, when pregnant women were presumably exposed to environmental heat. H4C3 plays a critical role in nucleosome formation and chromatin organisation, thereby regulating DNA replication and transcription, although the broader landscape of heat-induced epigenetic alterations in the placenta remains unknown. Supporting evidence comes from an epigenome-wide analysis of human placentas, which revealed associations between prenatal exposure to air pollutants and changes in placental DNA methylation. These methylation changes were linked to altered birth outcomes, including significant effects on genes related to neural development, immunity, and metabolism.

Moreover, intergenerational transmission of epigenetic modifications has been reported, whereby maternal exposure to environmental stressors negatively impacts infant health and well-being. Taken together, these findings suggest that heat exposure may have a substantial impact on the placental epigenome, potentially disrupting its functions and adversely affecting birth outcomes. This hypothesis warrants further investigation through large-scale studies.

What do we know about the heat effects on placental hormones?

Although animal studies have demonstrated that heat stress significantly elevates maternal hormones that induce labour, such as oxytocin and prostaglandins, less is understood about this effect in humans. Additionally, the direct impact of heat on essential human placental hormones that sustain pregnancy, such as human chorionic gonadotropin, oestrogen, progesterone, human placental lactogen, and placental growth hormone—has yet to be explored. However, studies on pregnant ewes have shown that chronic heat stress markedly decreased circulating progesterone and placental lactogen levels, which were linked to placental dysfunction.

In our study, we observed significant downregulation of the 15-hydroxyprostaglandin dehydrogenase (HPGD) gene in human preterm placentas exposed to warm temperatures. HPGD catalyses prostaglandin inactivation, suggesting that its downregulation due to heat exposure may promote premature labour. This hypothesis aligns with previous findings showing reduced placental HPGD expression in both animal and human preterm births. Further exploratory studies are necessary, as HPGD may represent a potential therapeutic target to mitigate heat stress-induced risk of preterm birth.

Conclusion

In this article, we highlighted the impact of environmental heat on placental biology and its implications for premature birth. Our findings underscore a critical gap in molecular evidence, particularly in humans, on how heat exposure reshapes the placental transcriptomic, epigenetic, and humoral landscapes that govern pregnancy outcomes. Given the placenta's central role in sustaining healthy gestation, advancing molecular research in this field is no longer optional but imperative. Unlocking these mechanisms will be vital not only for developing targeted therapeutics but also for updating global health policies to safeguard maternal and infant health in an era of accelerating climate change.

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