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REVIEW ARTICLE

An expert review of environmental heat exposure and stillbirth in the face of climate change: Clinical implications and priority issues

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Abstract

Exposure to extreme heat in pregnancy increases the risk of stillbirth. Progress in reducing stillbirth rates has stalled, and populations are increasingly exposed to high temperatures and climate events that may further undermine health strategies. This narrative review summarises the current clinical and epidemiological evidence of the impact of maternal heat exposure on stillbirth risk. Out of 20 studies, 19 found an association between heat and stillbirth risk. Recent studies based in low- to middle-income countries and tropical settings add to the existing literature to demonstrate that all populations are at risk. Additionally, both short-term heat exposure and whole-pregnancy heat exposure increase the risk of stillbirth. A definitive threshold of effect has not been identified, as most studies define exposure as above the 90th centile of the usual temperature for that population. Therefore, the association between heat and stillbirth has been found with exposures from as low as >12.64°C up to >46.4°C. The pathophysiological pathways by which maternal heat exposure may lead to stillbirth, based on human and animal studies, include both placental and embryonic or fetal impacts. Although evidence gaps remain and further research is needed to characterise these mechanistic pathways in more detail, preliminary evidence suggests epigenetic changes, alteration in imprinted genes, congenital abnormalities, reduction in placental blood flow, size and function all play a part. Finally, we explore this topic from a public health perspective; we discuss and evaluate the current public health guidance on minimising the risk of extreme heat in the community. There is limited pregnancy-specific guidance within heatwave planning, and no evidence-based interventions have been established to prevent poor pregnancy outcomes. We highlight priority research questions to move forward in the field and specifically note the urgent need for evidence-based interventions that are sustainable.

KEYWORDS
climate change, heat, heat stress, pregnancy, review, stillbirth

1 | INTRODUCTION

Approximately 2 million stillbirths, defined by the World Health Organization (WHO) as a fetal death after 28 weeks gestation but before or during birth, occur every year, with the majority of them occurring in Africa and South Asia.[1] Stillbirths have profound negative economic, social and psychological impacts on families and communities, and remain cloaked in stigma and shame.[2,3] Despite progress in many other aspects of maternal and infant health, only 32% of countries have a defined national stillbirth reduction target.[4] Most countries have experienced a reduction

in stillbirth rates since 2000 but the rate of improvement is less than other child mortality indicators.[5] Worryingly, in some countries, the number of stillbirths is increasing as birth rates increase faster than stillbirth rates decline,[1] with women with low socioeconomic status, lack of antenatal care, previous stillbirth, increasing maternal age and complicated pregnancies at most risk.[1,6]

The Intergovernmental Panel on Climate Change Sixth Assessment Report (2022) concluded that vulnerability to climatic hazards differs by region, and although all regions will experience higher temperatures and more frequent temperature extremes, certain regions will be more at risk (tens of thousands of additional heat-related deaths are predicted by 2100 especially in north, west and central Africa).[7]

There is growing interest in how climate change may affect birth outcomes and maternal health globally.[8–10] Exposure to high ambient temperature in pregnancy has been linked to adverse birth outcomes including congenital abnormalities,[11] miscarriage,[12] preterm birth[13–15] and low birth weight[16] as well as stillbirth.[17,18] These impacts have occurred at moderate levels of heat and in populations with temperate climates, as well as at higher levels of heat exposure in tropical and sub-tropical regions. Climate change is likely to affect birth outcomes also through other weather disasters and disruptions in access to health services.

This narrative review summarises the current epidemiological evidence of the association between environmental heat exposures and stillbirth, describes the potential mechanistic pathways, details existing guidance for pregnant women and identifies priority research areas for future work.

2 | ENVIRONMENTAL TEMPERATURE AND STILLBIRTH: EPIDEMIOLOGICAL EVIDENCE

Recent systematic reviews include those by Chersich et al.[19] on heat and adverse pregnancy outcomes (2020) and Sexton et al.[18] on heat and stillbirth (2021). Both of these reviews found good evidence of an increased risk of stillbirth at higher temperatures. Only one of 12 studies included in these reviews was conducted in a low- to middle-income country (LMIC, Ghana).[20] A search on the Embase database for studies published since the Sexton review identified a further eight studies on the association between heat and stillbirth, four of which were based in Africa or Asia.[21–24] In total, 19 of 20 studies found an association between heat exposure and stillbirth and one study found no association.

The previous reviews demonstrated that the association between temperature and stillbirth was most pronounced for exposures in the final week or month before birth, suggesting an acute effect of heat exposure. Fewer studies have examined the impacts of chronic exposures (i.e., high temperatures throughout the duration of pregnancy). Chersich et al.'s meta-analysis found that stillbirths increased 1.24-fold (95% CI 1.12–1.36) with exposure to high temperatures in the week leading up to birth, and 3.39-fold (2.33–4.96) with exposure during the third trimester or all of pregnancy.[19]

Four of only five studies conducted in LMICs have been recently published.[20–24] Nyadanu et al.[24] explored the impact of heat stress (defined by the Universal Thermal Climate Index, UTCI) on 5 961 328 births in Ghana from 2012 to 2020. Exposure to the 90th centile of UTCI versus the median (30.8°C vs. 28.8°C), for the whole of pregnancy, resulted in an 18% (95% CI 2%–36%) increased risk of stillbirth. Exposure to the 99th centile of UTCI (33.2°C vs. 28.8°C) for the whole of pregnancy protected against stillbirth, which suggests that women in this setting may only adapt their behaviours when heat exposure becomes unbearable.[24] In Iran, an area where temperature variation throughout the year is large and summer temperatures can reach as high as 50°C, two studies explored the impact of heat and stillbirth. Khodadadi et al.[23] found an increased risk of stillbirth in the last 2 weeks of pregnancy in those exposed to the 99th centile of heat stress (46.4°C) compared with the 75th centile (38.0°C), odds ratio (OR) of 2.0 (95% CI 1.0–4.2). In contrast, Ranjbaran et al.'s time-series study from Tehran based on data on 3460 stillbirths from 2015 to 2018 found no significant impact of heat, using a variety of different definitions for exposure.[22] McElroy et al.[21] used a time-stratified case-crossover design and Demographic Health Surveillance (DHS) data from 14 LMICs and found that stillbirth risk increased with exposure to maximum temperatures above 20°C. However, this study used DHS data where there can be uncertainty in the accuracy of exposure assignment (uncertain dates) and outcome (likely to include neonatal deaths).

In Western Australia, risk of stillbirth was found to increase by 19% (95% CI 17%–21%) when women were exposed to moderate heat stress (99th centile UTCI, 31.7°C) versus no thermal stress (50th centile UTCI, 13.9°C) throughout the last week of pregnancy, and by 41% (95% CI 38%–44%) when exposed to moderate heat stress throughout the last 2 weeks of pregnancy.[25] In Taiwan, Yang et al.[26] estimated that 2.64% of all stillbirths are attributable to high ambient temperature exposures (>29°C). They found that women are most susceptible to adverse heat effects in the third trimester of pregnancy, with a 2.4-fold (95% CI 1.19–4.8) increased risk of stillbirth when exposed to the 99th centile of monthly mean temperature (30.1°C) versus the optimal temperature (21°C) 0–3 months before delivery.

Four studies from the USA, all using very large data sets, found an increased risk of stillbirth with increasing temperature exposure.[27–30] Kanner et al.[27] analysed 112 005 pregnancy outcomes and found a four-fold increased risk of stillbirth for whole pregnancy exposure to temperatures >90th centile versus 10–90th centile (>12.64°C vs. 4.54°C–12.64°C), and a 7% (95% CI 4%–10%) increased risk with each 1°C increase during the final week of pregnancy. Richards et al.[30] looked at the impact of heatwaves (by various definitions), across six US states. Like Nyadanu et al.,[25] they found that the risk of stillbirth increased with the intensity and duration of the heat episode. Risk of stillbirth increased by 10% (95% CI 4%–17%) with every 1°C increase

in the 7-day average over the heatwave threshold. Two further studies from the USA both used a case-crossover study design. Here, a person's exposure levels on the days leading up to the health event ("case days") are compared with that same person's exposure levels on proximate days ("control days"), thereby implicitly controlling for confounding factors that are time-invariant.[31,32] Rammah et al.[28] found an increased odds of stillbirth (OR 1.45, 95% CI 1.18–1.77) associated with a 5.6°C increase in apparent temperature in the preceding week, and Savitz and Hu[29] found similar odds.

Overall, the new studies add several key points. There are now clear data from tropical and temperate regions demonstrating the impact of heat exposure on stillbirth risk, both acutely and chronically. As expected, variation in exposure metrics and methodologies prevents easy and clear summary statistics. However, it is clear from these studies that populations exposed to temperatures above the 90th centile of the usual temperature for that population are at increased risk. This association has been found with exposures from as low as >12.64°C up to >46.4°C. From these studies, taken together, where large data sets have been used and potential confounders controlled for, we find the evidence of the impact of heat on stillbirth to be robust.

Furthermore, some of these studies have explored specific characteristics that modify the impact of heat on stillbirth. For example, Savitz and Hu[29] found that when pregnant women were stratified by socio-economic status, the odds of stillbirth at high temperatures was over double that in the lowest socioeconomic status quartile versus the highest. Other risk groups identified in previous studies include term stillbirths,[25,33] male fetuses,[25,34] younger women,[25] non-white women,[25,28] and women living in rural areas.[21,24] Understanding these risk factors in more detail will aid in the development and implementation of targeted interventions to reduce the impacts of heat on stillbirth risk.

Few studies have considered the differential effects of heat exposure on different stillbirth outcomes. Stillbirth is a heterogeneous phenotype, and mechanisms are likely to differ by cause (e.g. infectious, congenital or placental cause) and gestational age. However, there are significant data limitations in determining heat effects. Relatively large data sets are needed to detect heat effects, and certainly when looking at different causes of stillbirth or effect modifiers. Additionally, stillbirths are underreported, particularly in low-resource settings. Also, heat exposure may increase the risk of early (clinically unobserved) pregnancy loss, which may pre-select conceptuses that have some degree of heat tolerance, but may result in longer-term health implications for the developing child.[35]

3 | HEAT STRAIN IN PREGNANCY AND THE RISK OF STILLBIRTH

Humans maintain their core temperature within a narrow range of 35.5–37.5°C, by ensuring that heat loss equals heat gain.[36,37] Heat gain occurs from both internal (metabolic) and external (environmental) sources and heat loss relies on both behavioural and physiological mechanisms. Although behavioural options are many, the physiological mechanisms to lose heat are limited to three—diversion of blood to the skin to increase radiative and convective heat loss, sweating to enable evaporative heat loss and reduction in metabolic rate to limit heat production.[37] A steady core temperature protects against fetal strain, preterm labour or stillbirth by ensuring optimal functioning of the many systems within the body, including both intra- and extra-cellularly. These include protein folding (hypothesised to increase the risk of congenital abnormalities and early pregnancy loss), catalytic enzyme actions, and maintenance of tight junctions between cells to preserve blood–brain and intestinal barrier integrity (loss of these barriers results in activation of the inflammatory cascade).[37]

There are multiple physiological changes that occur during a human pregnancy that could affect thermoregulation, visualised in Figure 1. Cardiac output and plasma volume increase by up to 50% by the third trimester and although red blood cells increase, there is a dilutional anaemia.[38] The increase in basal metabolic rate and decrease in body mass to surface area ratio is balanced by lowering of the sweat threshold and a steady decrease in core temperature as pregnancy progresses.[39]

There remains equipoise as to whether these physiological changes impair thermoregulation, but recent studies have demonstrated that, in humans, maintaining thermal homeostasis is no more challenging in pregnancy than when not pregnant.[39–41] However, as discussed below there are

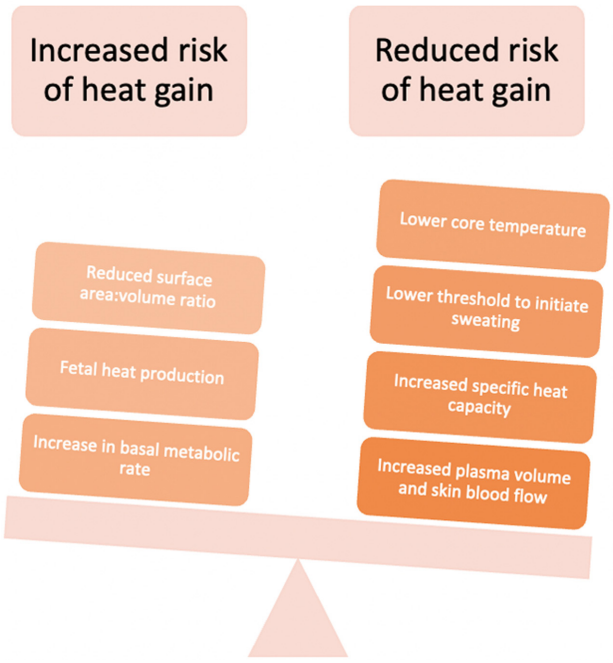

FIGURE 1 Representation of the physiological alterations in pregnancy that influence thermoregulation. Specific heat capacity refers to the amount of heat required to increase the temperature of 1 unit of mass by 1° Kelvin—therefore a higher specific heat capacity means more heat is needed to increase the temperature of a given mass.

several potential pathways implicated in the association between heat exposure and stillbirth, with maternal heat strain only being one of them.

4 | HYPOTHESISED PATHOPHYSIOLOGICAL MECHANISMS

It is estimated that over 40% of stillbirths globally are preventable with improved antenatal and intrapartum care.[1] Some of the known risk factors for stillbirth include: hypertension, diabetes, infections in the mother, and also fetal growth restriction and maternal undernutrition. Environmental factors known to cause stillbirth include household and outdoor air pollution and a range of chemical hazards.[42] However, no clear cause is found in approximately 30% of cases.[43] In this section we describe the key pathophysiological mechanisms proposed in the literature for the impact of heat on pregnancy, with a focus on those pathways relevant to stillbirth. These pathways include:

- congenital malformation[44]
- maternal heat strain[36,45]
- dehydration[46]
- reduction in placental blood flow[47,48]
- placental growth restriction[49]
- placental insufficiency[50]
- oxytocin and prostaglandin release.[51]

Most of these mechanisms although plausible from a theoretical and animal physiological understanding, remain hypothetical as detailed studies in humans are lacking.[39] It is important to note that although pathophysiological mechanisms of adverse pregnancy outcomes may overlap, it is likely that there are additional pathways to consider for each outcome. For example, details from experimental animal studies show that acute heat stress can reduce blood flow to the placenta by up to 30% (potentially a trigger for preterm labour or stillbirth), and when exposed to prolonged heat stress in late gestation, can decrease placental size and impair nutrient and oxygen transport in mammals (a potential mechanism for low birthweight or stillbirth).[52,53] Other data in experimental mammals reveal that cyclic heat stress during early gestation perturbs the expression of genes and proteins controlling nutrient transport and metabolic processes, including glucose and peptide transporters in the placenta.[54] Therefore, heat stress may reduce blood flow to the placenta, impair placental function and trigger small for gestational age, fetal growth restriction and/or preterm birth or stillbirth.

The upregulation of heat-shock proteins is also potentially implicated in the effects of heat stress/strain on pregnancy outcomes.[55] Heat-shock proteins, also known as molecular chaperones, are a broad group of inducible proteins, produced by cells as a response to any potentially damaging stimuli, and not specific to heat stress, e.g., they can be triggered by ischaemic or oxidative stress and often act as intercellular stabilisers.[56] Of note, they protect cellular protein synthesis machinery and avoid apoptosis and necrosis induced by stress stimuli. In heat acclimation, heat-shock protein levels increase in keeping with the phenotypical changes that are also induced (lowered core body temperature, cardiovascular stability, lowered sweating threshold and improved heat loss).[57,58] In pregnancy, there is no clear consensus on the role of heat-shock proteins,[59] although there is some evidence that they are in placentas from pregnancies with adverse pregnancy outcomes, such as small for gestational age[60,61] and possibly, preterm birth.[61–63] There are also changes in the abundance of cells positive for heat-shock proteins within the maternal decidua in cases of spontaneous pregnancy loss.[63] Heat and heat-shock proteins may promote proinflammatory cytokine release and tissue inflammation,[64–66] which are key triggers for parturition, and so may have implications for premature delivery in the context of heat and pregnancy.[67–69] Indeed, there are data suggesting that exposure to elevated temperatures in warm seasons near or at term, increases the risk of placental abruption.[70]

Recent work using transcriptomic analysis of the placenta has identified further pathways, including aberrant expression of genes and pathways implicated in nutrient sensing, protein synthesis and folding, mitochondrial function, and nutrient and vascular transport, which probably contribute to fetal outcomes in women exposed to heat stress during pregnancy.[71] These placental changes are consistent with molecular studies of the placenta in unexplained fetal growth restriction and pre-eclampsia (both risk factors for stillbirth).[72,73]

There is also a proposed role for epigenetic changes as being mediators of the effect of maternal heat strain on pregnancy outcomes. This is mostly extrapolated from experimental animal studies. The epigenome describes modifications to the DNA and DNA-associated proteins, which impact gene expression—genes may be switched on and off in different cell types and at different times.[74] Defective epigenetic changes can result in severe health implications, such as increased risk of type II diabetes, cardiovascular disease and metabolic disorders.[75–77] Evidence from mammalian studies indicates that epigenetic modifications are sensitive to heat exposure and potentially disrupt imprinted gene expression[78] and metabolic proteins,[79] and reduce antioxidant defence capacity among other effects.[80,81] In chick embryos exposed to heat stress, there are also changes in the activation of the heat-shock protein HSP70, which serves to stabilise the intracellular environment with potential implications for long-term heat vulnerability and resilience.[82] However, human data are still lacking and it is likely that the pathophysiological pathways are complex and interconnected (see Figure 2 for a simplified visualisation of hypothesised pathways). Moreover, the implications of these potential pathophysiological pathways for understanding impacts of heat stress and strain on human populations, remain unclear.

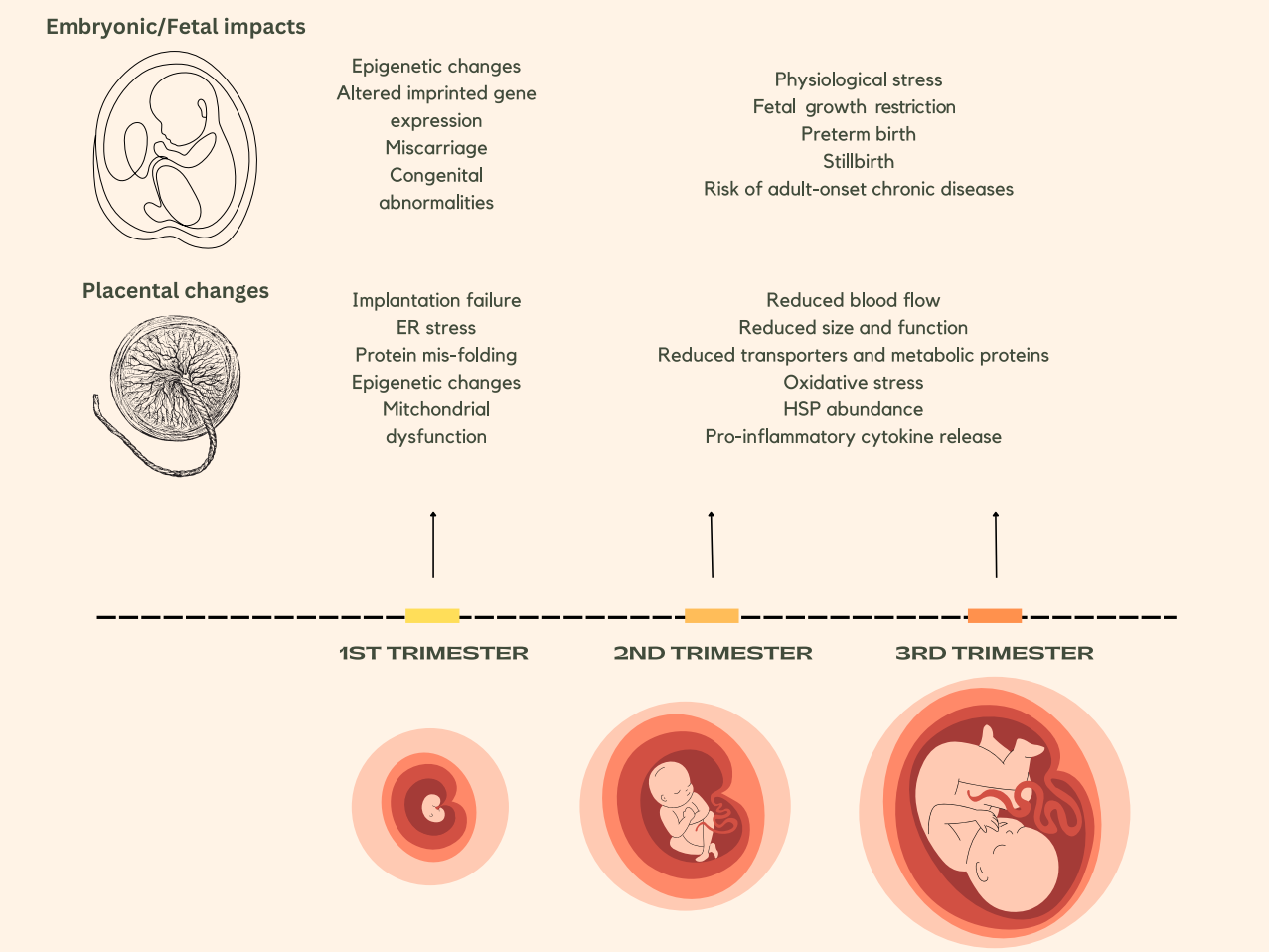

FIGURE 2 Hypothesised pathophysiological pathways of the impact of heat on the placenta and the fetus. Abbreviations: ER, endoplasmic reticulum; HSP, heat-shock proteins.

5 | CURRENT GUIDANCE: REDUCING THE HEAT RISK IN PREGNANCY

It is important that pregnant women understand the risks of exposure to high temperatures. There are several strategies for reducing the impacts of heat, including both health education and increasing access to cooling spaces. Although, to our knowledge, there is no specific guidance on reducing the impact of heat on stillbirth risk, broader measures to reduce the heat health risk in pregnancy are discussed here because they are potentially effective for all heat-related adverse birth outcomes.

Some guidance is targeted towards vulnerable populations identified as those who are at increased risk from heat, and with specific actions depending on those at risk, often targeted to healthcare workers or carers. UNICEF published *Protecting children from heat stress* report in May 2023, which includes some guidance on prevention and treatment of heat stress in pregnancy as well as in infants and children.[83] National agencies such as the CDC and UKHSA also provide specific advice for heat health protection. The WHO/World Meteorological Organisation recognise that local and national heat health action plans are important to prevent heat-related illness and mortality. Such plans include preparedness measures as well as just actions linked to heat alerts. Due to the increased concern about heat, there has been an increased focus on the built environment and how to reduce heat exposures through planning and housing design.

There also needs to be an increased awareness of heat risks among clinicians and healthcare workers. The International Federation of Gynecology and Obstetrics released a position statement committing to incorporating climate change into its *Education, Advocacy and Research Programs* going forward.[84]

Public health action to reduce the health impacts of heat (visualised in Figure 3) can be broadly considered as (1) public health messaging and awareness/individual behaviour change, (2) community-level interventions and (3) healthcare provider interventions.[85] Heat health warning systems have been shown to be effective in high-income countries,[86] and ongoing work shows promising evidence from LMICs.[87,88] However of note, this evidence relates to evaluation of impact on the rate of mortality in the general population and to date there have been no evaluations of the impact of these

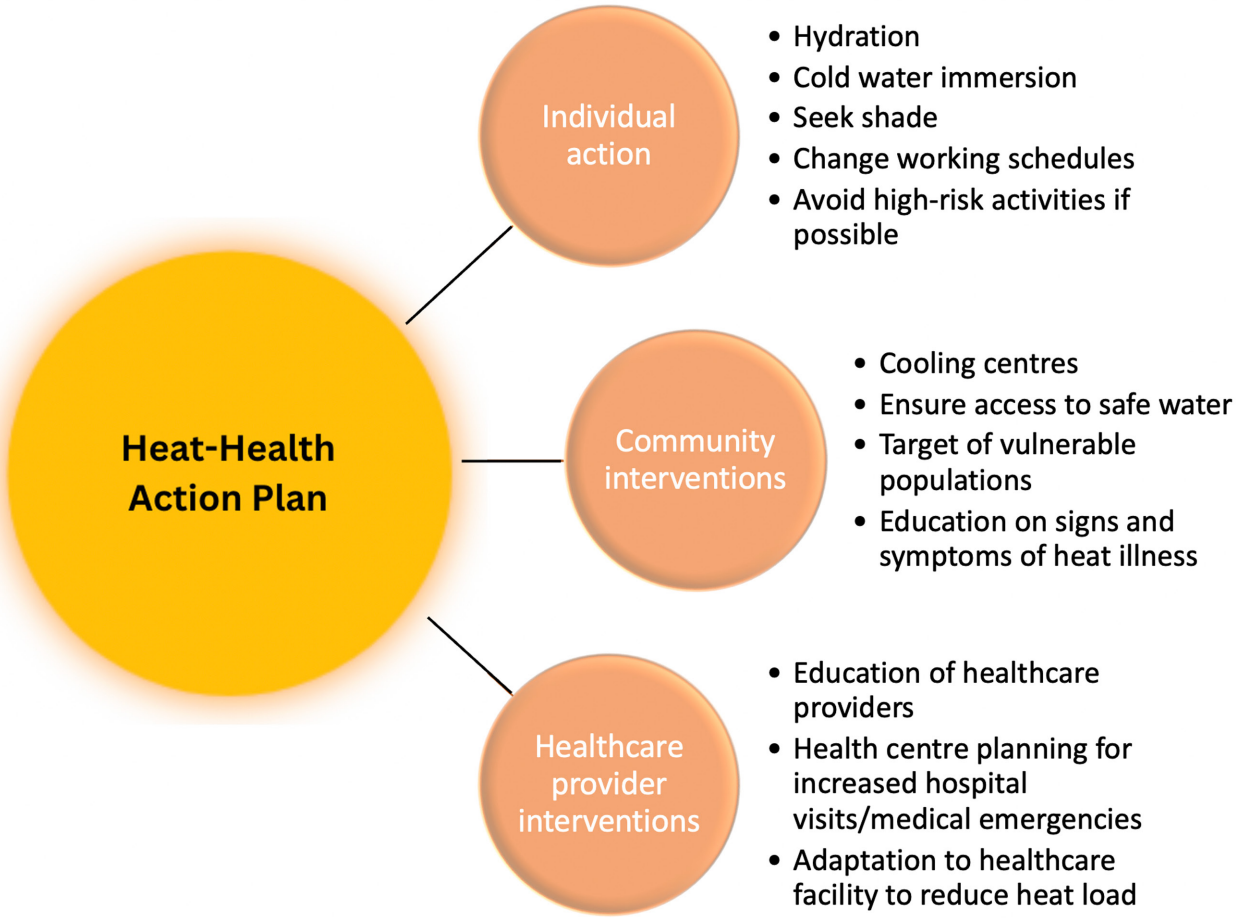

FIGURE 3 Visualisation of short-term action to reduce the adverse effects of heat on the general population (not pregnancy specific).

action plans for heat-related morbidity or pregnancy-related complications.

Key take-home messages for healthcare workers caring for pregnant women are that there remains poor awareness of the health risks of heat among healthcare professionals, pregnant people and their families. This should be addressed as a priority in the light of increasing exposure to heat. Special consideration, such as specific targeted advice or referral to high-risk clinics, for at-risk pregnant women should include those with chronic health conditions, high levels of exposure (occupational exposures, high indoor temperatures) and socio-economic constraints that limit heat avoidance activities (e.g. access to cooling from fans or air conditioning units, manual workers etc.).

6 | KEY GAPS AND PRIORITY AREAS FOR ONGOING WORK WITH A CLEAR CLINICAL NEED

There is good evidence that high ambient temperatures are harmful to pregnancy, but the magnitude of these effects remains largely unknown. This is now a priority for maternal health communities, and several new projects to explore these biological mechanisms have been funded in this area in 2023 by the Wellcome Trust.[89]

For clinicians, strategies to slow global warming (mitigation), beyond individual actions and advocacy efforts, are beyond the scope of the typical healthcare worker roles, although involvement in action to reduce harmful greenhouse gas emissions associated with the healthcare system should be encouraged. Healthcare workers should, however, support and identify effective adaptation strategies for their patients, working with women and communities to minimise the effects of prolonged heat exposure on pregnancies. Clinical research needs to better recognise who is vulnerable, discover what gestational age window is at particular risk, and assess the clinical and cost-effectiveness of adaptation strategies (see Table 1 for expanded research priorities).

Central to these efforts must be a focus on equity, with the research led by and carried out in communities and countries most at risk of extreme heat exposure. The paucity of high-quality data from LMICs has been highlighted from this review. There are several large, well-dated and complete pregnancy cohorts that have been established over the past 15 years in LMICs and there is an opportunity to leverage these cohorts to answer ecological exposures such as heat, with many of these cohorts also having large biorepositories

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TABLE 1 Priority research questions.

Clinical	Policy
What are the at-risk windows throughout pregnancy?	What are the best heat or heat stress metrics to assess the impact on stillbirths?
Can the mechanistic pathways be clearly understood and potentially manipulated to develop an intervention?	Do current heat action plans reduce health impacts of heat on pregnancy?
Are individual actions to reduce heat exposure effective to reduce the risk of stillbirth?	Are community-level interventions effective for pregnant women?
Can at-risk women be identified early in pregnancy?	Does improved climate resilience within the health system translate into improved patient care?

to test hypotheses as they emerge from the ongoing work in this space.

7 | CONCLUSION

Ultimately, action to limit global warming remains the number one priority to reduce exposure to extreme heat and other climate hazards and so limit the health impacts of climate change. Second, universal access to sustainable cooling is essential going forward. Finally, long-term adaptation efforts to reduce the impact of heat on stillbirth must consider the global, regional and local spatial inequality in exposure and the complex interplay of social and economic factors that are often missing in terms not only of identifying those most at risk, but also in developing effective interventions.

AUTHOR CONTRIBUTIONS

AB conceptualised and undertook the systematic review and co-wrote the initial draft. CP, ANS-P and JEH co-wrote the initial draft and edited the manuscript. UO, RC, SH and SK reviewed and edited the manuscript.

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