Fetal and neonatal hyperthermia

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Abstract

This article explores the concerns related to adverse neurological outcomes associated with fetal and neonatal hyperthermia. Maternal temperature is the most important determinant of fetal temperature; here we draw attention to the changing epidemiology of intrapartum maternal pyrexia and consequent fetal hyperthermia, particularly its association with labour epidural analgesia. The implications of potential adverse neonatal outcomes demand a greater understanding of the pathophysiology of intrapartum maternal fever and exploration of monitoring, preventative and therapeutic options encompassing the modern obstetric, anaesthetic and neonatal practice.

Keywords adverse outcomes; epidural; maternal pyrexia; neonate

Background

Modest therapeutic hypothermia (TH) (core temperature of 33–34 °C) in neonates with moderate to severe hypoxic–ischaemic encephalopathy (HIE) is now regarded as a standard of care. It improves outcomes, reducing the risk of death and neurodisability. However, when newborns with hypoxic–ischaemic encephalopathy were stratified by the severity of the initial amplitude integrated EEG (aEEG), the neuroprotective effect was statistically significant only in the group of infants with moderately abnormal initial aEEG. This suggests that the therapeutic effect is partly limited by the extent and severity of the initial brain injury. Even in the select group of neonates with moderate HIE, where TH has proven benefits, the effect is best described as modest. The short therapeutic window (3–6 hours) to achieve target temperature for optimum neuroprotection and the decremental neuroprotective effect of TH over time poses significant logistic challenge in managing infants born outside the cooling centre.

TH remains the only proven therapeutic option available after birth and many studies are currently exploring the use of adjuncts to TH to further improve outcomes. Animal studies suggest that the most powerful effect of TH is in the intra-ischaemic phase. This is, of course, not possible to institute in clinical practice as most hypoxic–ischaemic events occur in-utero and cooling the fetus directly at this time would be impractical.

In this context, it seems sensible to explore the question, if hypothermia is neuroprotective, could fetal hyperthermia be damaging? If the latter is true, then the prevention of fetal hyperthermia assumes a greater significance. There is evidence from animal and human studies that maternal pyrexia, a direct determinant of fetal hyperthermia, is associated with increased incidence of adverse neonatal outcomes. While infection remains an important cause of maternal fever, epidural analgesia, a popular pain relief in labour in developed countries, is emerging as the commonest association of intrapartum maternal pyrexia. The underlying cause of this association is not fully understood. Nevertheless, it has inadvertently provided researchers with a frequently occurring model of maternal pyrexia in clinical practice, which enables observation of its effect on the fetus and the neonate, and exploration of novel therapeutic options.

The implications of potential adverse neonatal outcomes demand a greater understanding of the pathophysiology of intrapartum maternal fever and the review explores this and highlights monitoring, preventative and therapeutic options for modern obstetric, anaesthetic and neonatal practitioners.

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Adverse effects of hyperthermia during neuronal hypoxia/ischaemia – evidence from animal and adult human studies

Several animal and human studies have examined the impact of hyperthermia on neuronal injury at or following a hypoxic–ischaemic insult. Rats subjected to intra-ischaemic hyperthermia suffered a significantly increased extent and severity of brain damage after the insult. Canine studies have demonstrated that an increase in brain temperature of only 1–2 °C during the hypoxic–ischaemic insult result in significant worsening in both post-ischaemic neurological function and cerebral histopathology. Infarct volume, and the number of ischaemic neurones are increased even when the hyperthermia occurs greater than 24 hours after the ischaemic event.

Pyrexia after a stroke in human subjects is associated with increased infarct size and worse outcomes. A meta-analysis of the effect of post-stroke pyrexia in stroke patients demonstrated a marked increase in mortality and morbidity in the group that developed pyrexia following the stroke. A number of studies suggest that earlier the hyperthermia following stroke, the worse the outcome.

The mechanism of neuronal injury associated with hyperthermia is not well understood and is likely to be a multifactorial process. The concentration of excitotoxic neurotransmitters such as glutamate and glycine are higher and persist for longer in the basal ganglia of rats subjected to ischaemia and hyperthermia when compared to those where normothermia was maintained. Free oxygen radical production in cerebral extracellular fluid is higher when an ischaemic event is associated with hyperthermia. Other mechanisms that may explain accelerated neuronal injury in experimental animal models include increased permeability of blood–brain barrier, activation of proteases resulting in degradation of cellular cytoskeletons and increase in the number of post ischaemic neuronal depolarisations.

Neuronal injury secondary to hyperthermia – could there be a threshold effect?

While confusion, stupor and a lowered threshold for convulsions are well known to be associated with high fever, permanent brain injury related to fever alone is perceived as uncommon and is often attributed to the underlying disease pathology. The evidence from animal studies suggest that the threshold at which

neuronal injury occurs following a precipitating event such as a hypoxic–ischaemic or infective event may be lowered by concomitant hyperthermia and may be critical in determining the extent of the neuronal injury. Normal labour is associated with short periods of ischaemia and hypoxia in the fetus due to intermittent interruption of placental blood flow secondary to uterine contractions. This is usually well tolerated but may cross the critical threshold in the presence of fetal hyperthermia and additional placental dysfunction. An animal study in the 1970s investigating the effect of hyperthermia in pregnant baboons found that a profound acidosis and hypoxia developed in the fetus. Impey et al., examining the relationship between intrapartum fever, neonatal acidosis, and the risk of neonatal encephalopathy, found that the absolute risk of neonatal encephalopathy in the presence of both maternal intrapartum fever and cord acidosis was 12.5%, when compared to 1.58% with acidosis alone, 1.13% with fever alone and 0.12% when none of these risk factors were present. Unfortunately, hypoxic–ischaemic events in labour are not always predictable and therefore vigilance and control of fetal temperature assumes greater significance.

Of greater concern is the result of a recently published study by Seri et al. that conclusively proves that the adverse effects of perinatal hyperthermia on neuronal injury is independent of the other risk factors. They examined the effect of hyperthermia in a rat model of perinatal inflammation and hypoxia. Twenty rats received either a single injection of *Escherichia coli* lipopolysaccharide (LPS) endotoxin or saline placebo in late pregnancy and then subjected to hypoxia soon after birth. The newborn rats were then subjected to either a 2-hour period of moderate hyperthermia (39 °C) or normothermia. Brain tissue examination on day 5 of sacrificed animals showed that while LPS alone or in combination of hypoxia was well tolerated, the additional stress of moderate hyperthermia significantly increased the brain reactive nitrogen species, caspase-3 activity, and number of apoptotic cells in the CA1 region of the hippocampus.

What controls the fetal temperature? – understanding the feto-maternal temperature relationship

Like the mother, the fetus constantly generates heat during the process of metabolism, which must be dissipated to the environment if a constant temperature is to be maintained. Unlike the mother, the fetus is not in control of its own thermoregulation. Much of it relies on heat exchange through the placenta and maternal circulation (85%) while some heat (15%) is lost by convection through the amniotic fluid. The second law of thermodynamics dictates that in order for the heat to move from the fetus to its mother, there must be a temperature gradient in that direction, with fetus being warmer than its mother. Experimental studies in the 1950's confirmed this hypothesis when they observed that the fetal rectal temperature was approximately 0.5–1 °C higher than the maternal rectal temperature.

Later, Macaulay and colleagues, using a specially designed probe, measured uterine wall and fetal skin temperatures simultaneously alongside routine 4-hourly oral temperatures in women with labour epidural analgesia. There was a clear gradient between the fetal skin temperature, the intrauterine temperature and the maternal oral temperature. While maternal oral temperature measurements seriously underestimated this, in 30% of fetuses the maximal fetal skin temperature was greater than 38 °C and in 9% it exceeded 39 °C. Considering that fetal core temperature exceeds its skin temperature by an average of 0.75 °C, it is conceivable that in some cases, the fetal brain temperature may have reached close to 40 °C. Banerjee et al., in a subsequent study of meticulous temperature measurements of the human mother and fetus in labour, reported that while oral temperature measurements correlated well with intrauterine temperature measurements, it tended to underestimate the latter by approximately 0.8 °C. This suggests that, clinicians often underestimate the incidence and the effect of mild maternal pyrexia on fetal brain temperature. In an observational study, Perlman reported that nearly half of all neonates born to febrile mothers and requiring NICU admission had a rectal temperature over 38 °C and in 11.5% of cases it was over 39 °C.

In conclusion, while conventionally measured maternal temperature in labour might underestimate the true incidence, the detection of maternal pyrexia in routine clinical practice is a strong proxy for fetal hyperthermia. If the effect of maternal pyrexia and consequent fetal brain hyperthermia has a threshold and incremental effect on neuronal injury related to unexpected hypoxic–ischaemic events, then greater emphasis must be placed in the early detection and treatment of maternal fever in labour.

Changing epidemiology of intrapartum maternal pyrexia – the link with the use of epidural analgesia in labour

While infection remains an important cause, the commonest association of intrapartum maternal pyrexia in developed countries is the use of epidural analgesia in labour. Fusi et al. in 1989 first reported this finding prospectively, comparing a group of women with epidural analgesia against a control group using pethidine analgesia. Since then, numerous observational studies have confirmed this association. The proportion of women with epidural analgesia who develop an intrapartum fever $\geq$38 °C is reported to be between 6% and 40%, with nulliparous women being the most at risk. The potential for a pain-free childbirth has reshaped the expectation of women in labour, and as a result, epidural uptake in the developed countries has increased dramatically over the last two decades. It is estimated that an extra 15% of women will become febrile in labour related to epidural use. The proportion of women developing fever also rises with increased duration of epidural use. In fact, 95% of maternal fever in term labour is observed in women using epidural analgesia.

However, due to the ethical difficulties of randomising women to epidural and non-epidural groups, most research to date has been observational and thereby posing difficulties in firmly establishing a causal link between epidural use in labour and maternal pyrexia. In non-randomised trials, self-selecting cohort of women who receive epidural analgesia have confounding factors that may also lead to a temperature rise such as a longer duration of labour, prolonged rupture of membranes and a higher number of intrapartum vaginal examinations. A randomised controlled trial that used an intention to treat analysis, demonstrated a much higher incidence of fever in nulliparous women in the epidural group (24%) compared to the non-epidural group (5%), despite a high crossover rate from the