**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| Steven A Ringer MD PhD | Date Submitted for review: 10-05-09 |

**Clinical question.**

In neonates born to febrile mothers (P) does intervention to normalize temperature (I), compared to standard care (C) improve outcome (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention therapy**

**State if this is a proposed new topic or revision of existing worksheet:** New but a 2005 worksheet examined Hyperthermia in the neonate.

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

- **Fever, Labor, Obstetric, Complications** OVID 75 papers, including both proposed mechanism and effect on neonatal outcome. One paper on potential benefit of treatment, randomized trial merits further review, additional 7 papers merit further review
- **Pregnancy/ Maternal Fever, Inflammatory response** OVID 1737 papers Add Newborn 9
- **Pregnancy, Newborn, Fever, Therapeutics** OVID 170 papers
- **Therapeutics, Fever, Newborn** OVID 12 papers
- **Treatment Outcome, Labor, Obstetric, Fever** OVID 5 papers, none relevant

**Epidural fever and Neonatal Outcome** OVID 10 papers all merit further review

**Fever, Treatment, Neonatal outcome** OVID 13 papers, only 1 merits further review, already represented in above lists

**Chorioamnionitis, Neonatal outcome** OVID 22 papers, 9 relevant (merit further review) with at least 4 focusing on inflammatory response and impact on outcome

**Maternal Fever, Neonatal Outcome** OVID 587 papers mostly about outcome related to infection. If restricted to **Treatment Outcome** 173 papers 7 merit further review, most not useful

**Inflammatory Response, Maternal fever or pregnancy** OVID 1775 papers, restrict to **Neonatal outcome**, 9 papers, 6 useful for further review

**Epidural fever, Neonatal Outcome** PUBMED 16 papers None different from OVID

**Labor, Obstetric, Complications, Fever** PUBMED 127 references Add Newborn 57 references

I also have a PhD dissertation Elizabeth A. Greenwell 2008 Harvard School of Public Health, “The Influence of Pregnancy and Perinatal Risk Factors on Adverse Neonatal Outcome” which includes extensive review of the impact of maternal fever on neonatal outcome and discussion of potential mechanisms, and bibliography that includes 88 references of which 28 merit further review.

**EMBASE** Labor, Complications, Fever 11 References

- Labor, pyrexia, Newborn 138 references
- Labor, complications, brain injury, pyrexia 23 references

**ECC Endnote** Fever, Labor 16 references, 8 unique

All searches current through 9/26/09

- **State inclusion and exclusion criteria**

Newborns. In Ovid there are age ranges in the search criteria, including “Birth to 23 Months”. This was used as a search or inclusion criterion in order to find papers related to Newborns.

Exclusion criteria Infection excluded except in a two searches and specifically included (chorioamnionitis) in one. Much of literature relates to fever due to maternal infection. I excluded papers in which the infants themselves were infected,, or those in which maternal infection was proven or a predominant factor as an etiology of fever

Non –English papers were not excluded, Animal studies were included. Studies on effect of fever on adults were excluded as there is no direct clinical analogue

- **Number of articles/sources meeting criteria for further review:**

After initial screening for applicability and overlap between searches, there are 59 papers that merit further review for possible inclusion in the data analysis
# Summary of evidence

## Evidence Supporting Clinical Question

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<th>Level of Evidence</th>
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<td>Perlman 1999</td>
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<td>Lieberman 2000E</td>
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<td>Smulian 2003E</td>
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<td>Petrova 2001E</td>
<td>Lieberman, Lang 2000E</td>
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<td>Yancey 2001E</td>
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<td>Leighton 2002E</td>
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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
# Evidence Neutral to Clinical question

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# Evidence Opposing Clinical Question

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A = Return of spontaneous circulation  
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Italics = Animal studies
Fever is a common complication of labor, occurring in as many as 4-5% of women. Fever related to maternal infection (chorioamnionitis) increases the risk of fetal and neonatal infection, but it is clear that some {Amenttaku and Mulik 2007, Churgay, et al 1994, LOE 5}, if not most fever in labor is not infectious {Maayan-Metzger et al, 2006 LOE 5, Mantha et al 2008, LOE 2, Vinson et al 1993, LOE3}, and much of it is related to the use of narcotic analgesics and especially epidural anesthesia {Alexander and Alexander 2005 LOE 5, Fusi, et al 1989 LOE5, }; with which upto 15% of women develop a fever {Yancey et al 2001, LOE 3}. In this subset, the hyperthermia occurs soon after the epidural anesthesia is administered {Goetzl et al 2007, LOE 2}. The mechanism that results in fever is not clear, and some investigators have concluded that fever is normal in labor, reduced by commonly used low dose opioid analgesics but simply not suppressed by epidural anesthesia {Evron, et al 2008, LOE 5} while others refute this {Gross, et al 2002, LOE5}. Many investigators believe that the fever results from abnormal elaboration of cytokines in the maternal circulation {Mouihate et al 2002 LOE 5, Shalak et al 2002 LOE 4, Smulian et al 2003}. These cytokines have the potential to affect the fetus and result in neonatal complications.

Fetal temperature exceeds maternal temperature by as much as 1 degree C {Miller et al 2007 LOE 5,}, and for any level of maternal fever the impact on the fetus is greater. Several studies have demonstrated an association between maternal fever and adverse outcomes, including neonatal depression and encephalopathy {Perlman 1999 LOE 4, Impey et al 2001, LOE5, Leighton et al 2002 LOE 5,}, seizures {Lieberman et al 2000 LOE 4} and other negative effects {Adamson et al 1995 LOE 4, Banerjee et al, 2004 LOE 5, Blume et al 2008, LOE 5, Goodlin and Chapin 1982, LOE 4, Jordan et al 2001 LOE5, Lieberman et al 2000, LOE 5, Poulain et al 1990a, 1990b, LOE 4 }. Studies in baboons have demonstrated fetal deterioration during maternal fever {Morishima et al 1975, LOE 5}. Neonatal fever after birth has also been associated with negative effects {Shalak et al 2005 LOE4}, but not in all studies {Badawi et al 1998 LOE 4}. One hallmark study concluded that the association between maternal fever and low Apgars/cerebral palsy is due to infection (chorioamnionitis), not fever alone {Grether and Nelson 1997, LOE 2}, while a study demonstrating increased morbidity and mortality could not distinguish the effects of fever from those of maternal infection {Petrova et al 2001, LOE 3}

By treating maternal fever, fetal hyperthermia may be decreased or eliminated, although a small RCT showed no impact of acetaminophen on fever curves {Goetzl, 2004, LOE 2}. There are no studies directly examining the effect of fever reduction on neonatal outcome in either the short or long term. The closest inference is that hyperthermia during reperfusion following hypoxia is associated with increased neuronal injury in humans {Laptook et al 2008}, an effect that has been reduced by antipyretic treatment in animal studies {Coimbra et al 1996 LOE 5}.

If maternal fever results in even higher fetal hyperthermia and such fetal hyperthermia is associated with a variety of adverse fetal/neonatal outcomes, it is plausible to consider treatment aimed at reducing maternal fever in labor. Such direct treatment of fever is not associated with significant complications in other settings, as long as the administered doses of acetaminophen or other agents are carefully monitored, which suggests that the potential benefit of treatment may outweigh the risks. Only a randomized trial could adequately evaluate this question.

Along with the lack of primary information on the effectiveness of antipyretic therapy, several other knowledge gaps exist. The etiology of maternal fever is not known, and nor is the mechanism by which this can result in fetal/neonatal complications. Simple antipyretic therapy might blunt the fever without impacting the production of cytokines, and thus might have no impact on reducing fetal injury. Some fever during labor is the result of maternal infection, and this is often the only historical risk factor that prompts neonatal evaluation and prophylactic treatment. If fever is treated during labor, or antipyretic agents administered prophylactically, this important clinical marker will be altered or eliminated. To date studies have shown that non-infectious fever due to epidural anesthesia actually increases the rate of maternal antibiotic treatment and neonatal sepsis evaluation {Goetzl et al 2003, LOE 5, Goetzl et al 2001, LOE 2, Lieberman et al, 1997 LOE 5}. Any treatment plan would have to be designed to avoid this potential masking of infection, or have a plausible means of incorporating this factor into neonatal evaluation and treatment.

Acknowledgements:


**Citation List**


   **LOE 4  Fair Quality Supportive**
   **Comment:** A retrospective case control study of term infants that identified association between maternal pyrexia and moderate to severe neonatal encephalopathy. This is supportive evidence that fever alone can result in untoward neonatal outcome.


   Not included in reference grids.

   **Comment:** A useful review that describes the association of epidural anesthesia with fever and concludes that the risk of adverse effects on the fetus are unlikely. Not included in reference grids.


   Not included in reference grids.

   **Comment:** A review of causes of maternal fever that concludes that many causes of fever are non infectious and that these fevers can still pose a risk for both the mother and the fetus.


   **LOE 4 Poor Quality Neutral to Question**

   **Comment:** Unmatched case control study of infants with moderate to severe neonatal encephalopathy that identifies maternal pyrexia among the three factors most highly associated with neonatal encephalopathy. The pyrexia did not have to occur in the intrapartum period.


   **LOE 5 Not included in reference grids.**
Comment: Retrospective review: The occurrence of maternal fever leads to a need for neonatal evaluation, but the use of intrapartum antibiotic therapy reduced that need. Paper does not address relation with neonatal encephalopathy.


LOE 5 Poor Quality Supportive

Comment: This paper was motivated by a preexisting conclusion that maternal fever in labor results in adverse immediate and long term neonatal outcomes. This study defines the relation between maternal temperature at different sites and intrauterine temperature. The best indicator of intrauterine temperature is maternal oral temperature, which is about 0.8 degrees (C) lower than intrauterine.


Comment: Not included in reference grids.


LOE5 Fair Quality Supportive

Comment: Case control study examining 8 years of data on term singeltons in Washington State. They found independent association between either intrapartum fever > 38 degrees or chorioamnionitis and the an increased risk of the diagnosis of encephalopathy in the newborn


Not included in reference grids.

Comment: A review of newer epidural anesthesia, they conclude that while limited neonatal effects have been documented, the transient maternal hypotension and increased fetal heart rate have the -potential for effects. They do no mention fever as a prominent complication.


LOE 5 Poor Quality Supportive
Comment: This retrospective record review identified the fact that the diagnosis of maternal infection and therefore increased sepsis risk in the newborn can not be reliably made on the basis of fever alone, as there are other causes (most prominently the use of epidural anesthesia).


LOE 5 Fair Quality Supportive

Comment: Animal study in rats. following an experimental ischemic insult, the core temperature in rats increases. Treatment with an antipyretic reduces temperatures to normal values, and this markedly reduces the neuronal damage, similar results to cooling to normal temperatures. Avoidance of hyperthermia reduces ischemic injury.


LOE 5 Poor Quality Supportive


LOE 2 Poor Quality Neutral to question

Comment: This RCT exmained different epidural anesthesia regimens and the relationship to fever during labor. They found less temperature elevation in the women whose treatment included low dose opioids. They suggest that low dose opioids suppress fever due to labor, and question the association between epidural anesthesia and maternal fever.


Not included in reference grids.

Comment: A early study of forty patients randomized to receive epidural or non epidural anesthesia. The results demonstrate that epidural anesthesia is associated with a significant increase in maternal temperature, independent of infection or other causes

Not included in reference grids.

Comment: Animal study in lambs that indicates that the CNS origin of fever is suppressed in newborns. Not directly relevant to question


LOE 5 Poor Quality Supportive

Comment: A large review of singletons pregnancies that demonstrated an association between epidural anesthesia and maternal antibiotic treatment for presumed chorioamnionitis, presumably a surrogate for maternal fever in labor. Not directly relevant, but bears on the question of whether it is fever alone, or an underlying cause of fever, that results in problems in the fetus or newborn.


LOE 2 Poor Quality Supportive

Comment: Large review of singleton term pregnancies that demonstrates association between epidural anesthesia and neonatal evaluation for sepsis (and not sepsis itself). While several risk factors for possible sepsis were increased in these pregnancies, the major factor was low grade fever associated with epidural anesthesia. As in other studies, this study is a further piece of evidence that most fever in labor is not related to infection.


LOE 1 Fair Quality Opposing

Comment: This is a critical study in addressing the question of this worksheet. This is a small RCT that found that prophylactic acetaminophen does not prevent epidural related fever. Thus, even if fever is non infectious in origin and is associated with increased risk of CNS effects in the newborn, the inability to prevent this fever (albeit in this small study) would mean that this risk (fever) can not be prevented and thus the question about preventing injury becomes moot.

LOE 2 Fair Quality Neutral

Comment: This large prospective study of women who received epidural anesthesia demonstrates that most women do not develop fever, but in those that do, the fever develops shortly after the anesthesia is administered. This has ramifications with respect to monitoring schemes and potential use of antipyretic therapy, should an effective antipyretic for this clinical condition be identified. Other than that there is no direct bearing on the question.


LOE 1 Fair Oppose/Neutral

Comment: RCT comparing treatment with high and low dose corticosteroid as antipyretic/anti-inflammatory agent for maternal fever. High dose steroids suppressed fever and inflammatory markers (compared with placebo). Increased incidence of asymptomatic neonatal bacteruria in high dose group, no demonstrable benefit for newborn.


LOE 4 Poor Quality Neutral

Comment: Further evidence in a small prospective analysis of 50 pregnancies and labors, of the association of fever with non-infectious etiology.


Not included in reference grids.

Comment: Editorial that reviews evidence on epidural anesthesia and fever


LOE 4 Fair Quality Neutral

Comment: Large population based case control study that demonstrated a significant increase in unexplained CP among normal birth weight children borne by mothers with fever >38 degrees C while in labor. In these cases, there was a significant increase in the number of indicators of maternal infection, and the conclusion was that it was exposure to the infection, and not the maternal fever per se, that resulted in the increase in CP.

LOE 5 Fair Quality Supportive

Comment: Large cohort design record review of over 1200 patients which demonstrate that women who receive epidural anesthesia do have an increased incidence of fever, debunking the contention that non-epidural anesthesia suppresses labor-related fever. This informs the question and identifies a major etiology for fever during labor.


LOE 5 Fair Quality Supportive

Comment: This large prospective cohort study of nearly 5000 low risk women in labor at or close to term demonstrates the strong association between maternal fever and the occurrence of neonatal encephalopathy, and association which persisted after controlling for a number of other variables. The adjusted odds ratio was 4.72. This is significant evidence of the association between maternal fever in labor and acute neonatal encephalopathy.


Comment: A comment on another paper noted below. Not included in reference grids.


LOE 5 Fair Quality Supportive

Comment: An observational study of infants enrolled in a major trial of cooling for hypoxic ischemic encephalopathy that examined temperatures in the control infants. Increased temperature was found to correlate with increased risk of death or disability. Whether the increased temperatures are a result of greater severity or the case of worse outcome is not clear, but the results appear to compliments some of the animal data that indicates a worse outcome with higher temperatures after controlled experimental injury.

Comment: A useful review that includes discussion and references on the association of epidural anesthesia and fever. No additional scientific data. Not included in reference grids.


Not included in reference grids
Comment: A useful review that includes discussion and references on the association of epidural anesthesia and fever. No additional scientific data.


LOE 4 Fair Quality Supportive
Comment: A case control study that examined all term infants born at a large maternal center over an 8 year period, and identified all cases of seizures not associated with either sepsis or meningitis. The 40 cases were matched to controls. Infants with seizures were more likely to have been born following maternal fever in labor. Fever > 100.4 degrees F was associated with a nearly four fold increase in the incidence of unexplained early seizures. This paper, while drawing on a small group of affected patients, is strong evidence of the association between non infectious maternal fever and identifiable neurologic morbidity in the newborn.


LOE 5 Fair Quality Supportive
Comment: In this study of 1218 nulliparous women with singelton term, low risk pregnancies, over 10% of women developed a fever greater than 100.4 degrees, and essentially all the febrile women had received epidural anesthesia. The babies of febrile women were more likely to have a lower 1 minute Apgar score, and hypotonia. IF maternal fever exceeded 101 degrees, the babies were more likely to require bag and mask ventilation and oxygen therapy. This study demonstrates the impact of maternal fever on at least transient neonatal problems.


LOE 5 Poor Quality Neutral
Comment: An earlier study demonstrating that almost 15% of women who receive epidural anesthesia will get a fever greater than 100.4 degrees, which led to increased evaluation of their infants for sepsis, without a change in the rate of sepsis itself.

Not included in reference grids.


LOE 5 Fair Quality Neutral

Comment: Retrospective study examining causes of intrapartum fever, demonstrated that it is most often not associated with infection. In this study of 330 cases, the short term outcome in the babies was not different in those borne by febrile mothers.


LOE 5 Fair Quality Supportive

Comment: A prospective RCT comparing intermittent vs. continuous epidural anesthesia that demonstrates less maternal fever in the intermittent group, with no difference in neonatal sepsis evaluation rates. Other measures of neonatal morbidity were not examined.


LOE 5 Poor Quality Neutral

Comment: Study in rats which shows that the febrile response to endotoxin is suppressed in pregnant rats, compared to virgin or lactating animals. No relation to question.


Not included in reference grids.

Comment: Animal study in guinea pigs showing that hyperthermia is teratogenic at different points in pregnancy even at relatively low doses (when compared to potential thermal doses in humans with fever. This suggests that the use of animal studies may overestimate the teratogenic potential of thermal
exposure. This has limited bearing on the question about exposure to maternal fever in labor (i.e., outside the time when teratogenicity might occur.


LOE 5 Good Quality Supportive

Comment: A primate study (baboon) which has several important findings. First, it clearly demonstrates the fact that the fetal temperature is significantly higher than the peripheral measurement of maternal fever. In addition, the induced hyperthermia resulted in a number of significant physiological aberrations in mother and fetus, several of which might be related to worse short and potentially long term neonatal outcomes.


Not included in reference grids.

Comment: Animal study that also demonstrates that the fever response in rats is blunted at term. and discerns the likely mechanism of this response, a decreased expression of the COX2 enzyme. The relevance to the question in the longer term is that this understanding might potentially lead to some effective, physiologically neutral antipyretic therapy for use during labor. Obviously, this is well in the future of the current state of the art and potential therapy.


Not included in reference grids.

Comment: Review of much of the literature to date on the impact of fever on neonatal outcomes No abstract available


LOE 4 Good Quality Supportive

Comment: A large review of cases that demonstrates the association of maternal fever with several markers of transient neonatal depression, including a 5 minute Apgar score less than 5 and the need for chest compressions after birth, evidence of at least transient moriety in the newborn exposed to maternal fever.

LOE 4 Fair Quality Supportive

Comment: A large retrospective cohort study examining over 11,000,000 singleton live births. The results show increased risk of early neonatal death related to infection, especially in term infants when maternal fever greater than 38 degrees was recorded. Fever was also a risk factor for respiratory disease and neonatal seizures. In this study, the role of infection as a cause of fever was much greater than in several other studies. It appears that when fever is a marker for infection, the risk of mortality is increased, while non-infectious fever noted in other studies is better correlated with CNS morbidity.


LOE 5 Poor Quality Neutral

Comment: This retrospective questionnaire study examined possible perinatal factors associated with a later diagnosis of ADHD in a child. While several of these factors are unrelated to fever, some, such as a flu-like illness around delivery, are fever associated. While not directly bearing on the question at hand, this suggests that additional studies examining the potential long term effects of maternal fever in labor might include ADHD as a possible outcome.


LOE 4 Fair Quality Supportive


LOE 4 Fair Quality Opposing

Comment: These related studies found fever as a risk factor for neonatal infection in a high percentage of cases. This highlights the importance of considering infection as a cause of maternal fever, even though many studies have demonstrated that most intrapartum fever is not infectious in origin.


LOE 4 Fair Quality Supportive

Comment: This large retrospective database review examined maternal fever in labor and found an association with epidural anesthesia, but also with longer labor and a greater likelihood of intervention. More abnormalities in fetal heart rate monitoring were found among febrile women, and their babies...
were more likely to require NICU admission. This is another study that supports the idea that maternal fever in and of itself increases transient neonatal problems.


LOE 5 Good Quality Supportive

Comment: This study prospectively examined inflammatory cytokine levels in infants exposed to clinical chorioamnionitis. Among the several cytokines examined, only IL-6 and RANTES were elevated in the exposed infants. While the elevated cytokine levels were not associated with birth depression, they were related to adverse neurologic outcomes including abnormal neurologic examinations, HIE and seizures. Since much of clinical chorioamnionitis is diagnosed on the basis of fever alone, it may be that these findings relate to fever rather than infection, although that cannot be determined from this study.


LOE 4 Fair Quality Supportive

Comment: This study examined temperature in infants after birth to determine the impact on neonatal outcome. Higher temperatures in the neonate were associated with increased likelihood of NICU admission and birth depression, but not with worse outcomes. Whether it was the fever itself or an underlying cause of fever that led to the results could not be determined.


Not included in reference grids.

Comment: A useful review, adds no additional data for evaluation.


Not included in reference grids.

Comment: Another study in rats demonstrating an attenuated fever response in rats at or near term pregnancy that might ultimately inform questions about how to treat intrapartum fever.


LOE 4 Fair Quality Supportive
Comment: A study of term pregnancies with fever in labor that demonstrates elevated levels of IL6 without a strong correlation to placental markers of infection. The results suggest, but certainly do not prove that fever itself leads to elevated levels of IL-6, and that this or other inflammatory cytokines might result in adverse neonatal outcome.


Not included in reference grids.

Comment: A review that highlights noninfectious etiology of much of intrapartum fever,


LOE 5 Fair Quality Opposing

Comment: A large retrospective review that demonstrates that chorioamnionitis and not epidural anesthesia is responsible for maternal fever during labor.


LOE 3 Fair Quality Supportive

Comment: Both retrospective review and a prospective cohort study, which show that the duration of epidural anesthesia is correlated with increased maternal temperature, and elevations in initial newborn temperature as well.


LOE 3 Fair Quality Supportive

Comment: another retrospective cohort study that demonstrates an association between epidural anesthesia and maternal fever, with no measured difference in short term neonatal outcome.