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Full Length Research Paper

Redistribution of fetal blood flow in response to an acute fever episode during pregnancy in comparison with malaria

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The objective of the study was to determine if maternal fever during pregnancy alter placental function and induce fetal hypoxia. 31 pregnancies complicated by fever were studied. Uterine (UTRI), umbilical (URI), fetal cerebral (CRI) Doppler resistance index and amniotic index were measured on admittance (day 0; d0) and after treatment and fever release (day 2 to 4; d2-4). From d0 to d2-4, UTRI decreased in 68% of the cases; the URI decreased in 40% of the cases, and the CRI and the C/U ratio decreased in 45% of the pregnancies. At delivery, complications were not more frequent than usual, while the rate of early uterine contraction (50%) and premature delivery (20%) were higher than usual. An episode of limited duration fever during pregnancy can trigger mild increase in uterine, umbilical and cerebral flow due to the decrease in vascular resistance in the corresponding areas UTRI, URI and CRI (in 68%, 40% and 45% of the cases, respectively).

Key words: Fever, fetus, uterine flow, umbilical flow, cerebral flow, Doppler, malaria.

INTRODUCTION

Previous studies have demonstrated that suffering from malaria during pregnancy induces placenta insufficiency, resulting in fetal abortion or death at the beginning of the pregnancy, and abnormal fetal heart rate and prematurity in the second part of the pregnancy (Arbeille et al., 2002). In these circumstances, umbilical blood flow is reduced and there is a concomitant increase in cerebral blood flow, resulting in a cerebral/umbilical resistance ratio (C/U) lower than 1.1; an indication of fetal hypoxia. Animal studies demonstrated that the fetal flow redistribution in favour of the fetal brain with a C/U ratio lower than 1.1 is associated with reduced fetal PO2 (Arbeille et al., 2005). In addition, reductions in the amniotic fluid index, which relates to a deterioration of the kidney function, have been observed (Arbeille et al., 2002; Carles et al., 2003). Pregnancies can also be complicated by other maternal pathologies which induce fever over several days, such as influenza, bronchitis and pyelonephritis. Animal studies have reported increases in uterine blood flow with hyperthermia, possibly due to an increased concentration of prostaglandin in the maternal circulation inducing vasodilation. Although fetal blood prostaglandin concentration levels were also found to be increased, fetal blood flow were not measured (Andrianikis et al., 1989). Indeed, it is not known whether in human, the potential changes in fetal blood flow with maternal infection are altered due to fever.

Therefore, the objective of this study was to assess changes in maternal uterine and fetal flow, in addition to monitoring amniotic fluid and fetal heart rate, during an episode of fever to determine whether exposure to increased core temperature or to an infectious agent could (a) alter placental function and induce fetal hypoxia, or (b) induce a cardiovascular response in the fetus directly triggered by the increase in core temperature.

METHODS

Thirty one pregnancies complicated by fever were assessed on admittance to the hospital (day 0) and after treatment and fever release (day 2 to 4). Uterine (UTRI), umbilical (URI) and fetal cerebral (CRI) Doppler resistance index, and amniotic fluid echographic index were measured as part of the protocol of fetal surveillance used in routine at the Hospital for these pathologies

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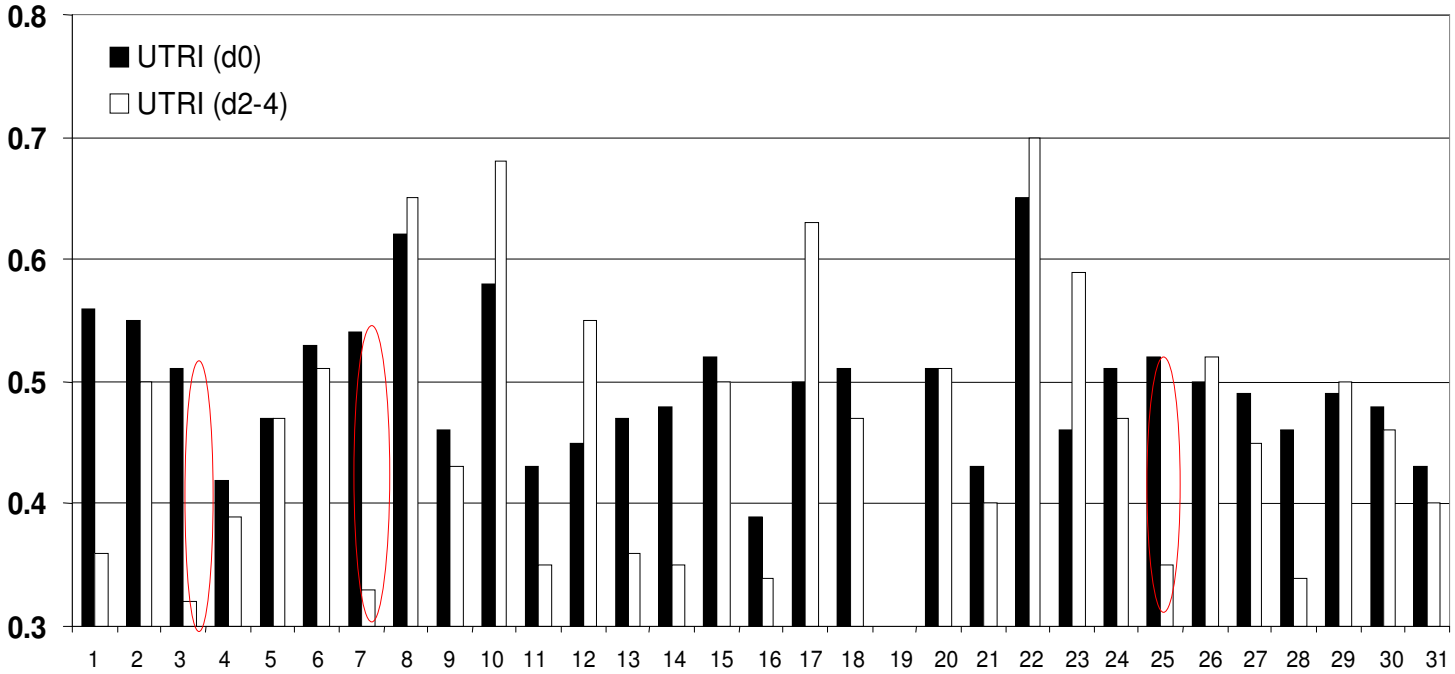

Figure 1. Uterine resistance index (UTRI) at admittance (d0) and after fever release (d2-4: day 2 to 4). The circles show examples of major drops in UTRI.

(Voluson 730 – General Electric). Measurements for the UTRI were taken on both the right and left uterine arteries, for the URI at the middle, free floating part of the chord, and for the CRI on the middle cerebral artery. The C/U ratio (CRI/URI) was calculated from Doppler indices using previously described methods (Arbeille et al., 2002). At any gestational age, in normal pregnancy, C/U is always higher than 1.1 which signifies that CRI is higher than URI. When C/U become lower than 1.1 (hypoxia), CRI decreases compare to URI, thus the cerebral flow increases compare to the umbilical one. C/U<1.1 signify that there is a flow redistribution in favour of the brain.

The amniotic fluid index was measured from the echography of the 4 quarters. The detection of early uterine contraction was made at admission with a cardiotocogram.

RESULTS

Thirty one pregnancies complicated by maternal fever (Dengue: 1, influenza: 7, bronchitis: 2, pyelonephritis: 12 and unknown etiology: 9) were included retrospectively into the study: From d0 to d2-4, the left and right UTRI remained inside the normal range but was decreased in 21 of the 31 (68%) pregnancies (-15±10%) ($p<0.05$) and increased in 7 (23%) of the cases (9±10%) (NS). UTRI decreased by more than 20% in 7/31 of the cases, and increased by more than 20% in 3/31 of the cases. (Figure 1).

URI and CRI remained also in the normal range and showed limited changes between d0 and day 2-4. The URI decreased in 12 of the 31 (39%) of the pregnancies (-9±6%) and increased in 18 (58%) cases (9±7%) ($p<0.05$). The URI increased (by more than 20%) in only 2/31 of the cases, and decreased by more than 20% in 3/31 of the cases. (Figures 2, 3).

The CRI decreased in 14 of the 31 (45%) of the pregnancies (-6±6%) (NS) and increased in the remaining 17 cases (8±7%) (NS). CRI decreased by more than 20% in 1/31 of the cases and increased by 2/31 cases.

The C/U decreased from -2 to -21% in 14/31 (45%) of the pregnancies (-9±6%) ($p<0.05$) and increased in 16 (8±7%) (NS) but remained in both cases above 1 at day 2-4 in all cases and above 1.1 in 28/31 cases both at d0 and d2-4. (Figure 4).

From d0 to d2-4, the C/U decreased by more than 15% in 6/31 and increased by more than 15% in 3/31 cases. The decrease in C/U concerned the highest C/U values at admittance thus none of the C/U entered frankly the hypoxic area at d2-4 (below 1.1). The amniotic fluid index did not change from d0 to d2-4.

At delivery, the rate of complication was not higher than in normal pregnancies (cesarean section, abnormal fetal heart rate and apgar score). Nevertheless, the rate of premature delivery was higher than usual in the Hospital centre (20% in pregnancies with fever vs 12% of the other pregnancies admitted) and the rate of early uterine contraction was higher than usually observed (more than 3 contraction every 10 min) in 50% of the cases.

The medication used was a conventional antibiotic therapy adapted to each of the pathology to which was added Paracetamol.

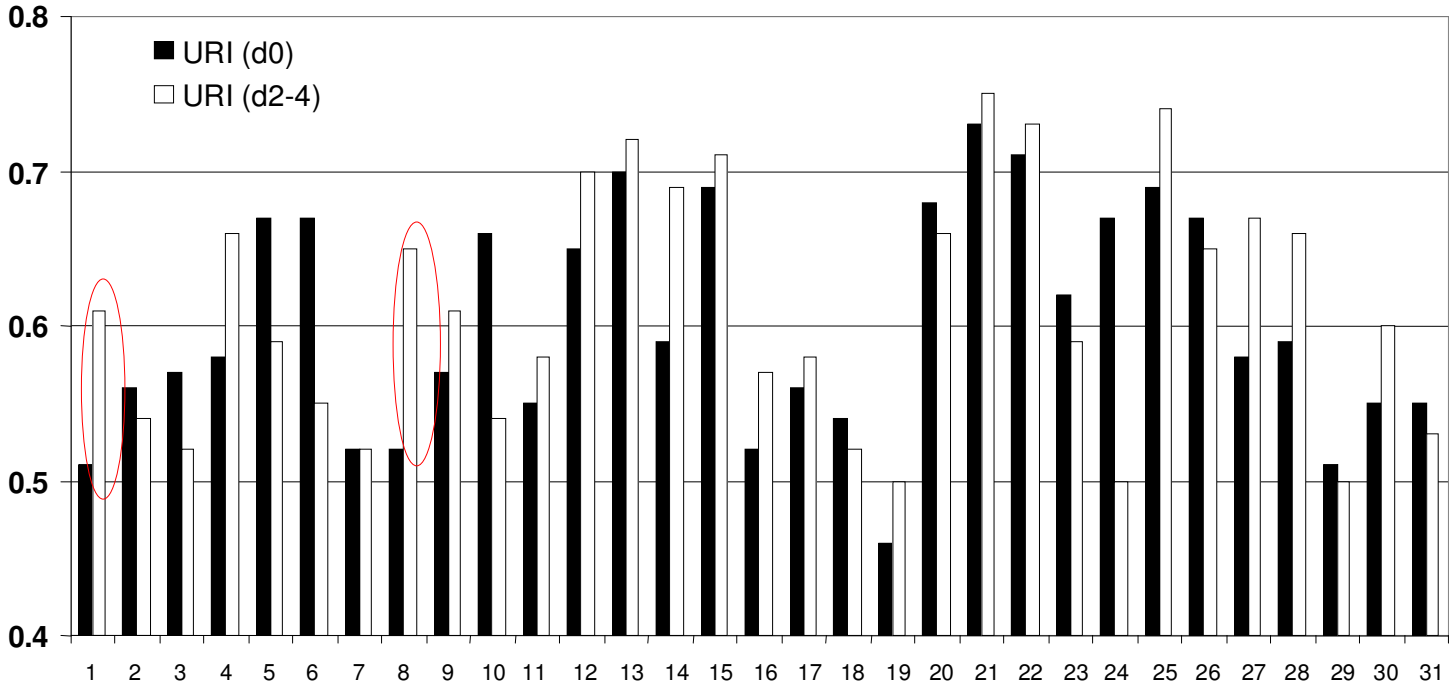

Figure 2. Umbilical resistance index (URI) at admittance (d0) and after fever release (d2-4: day 2 to 4). The circles show example of major increase in URI.

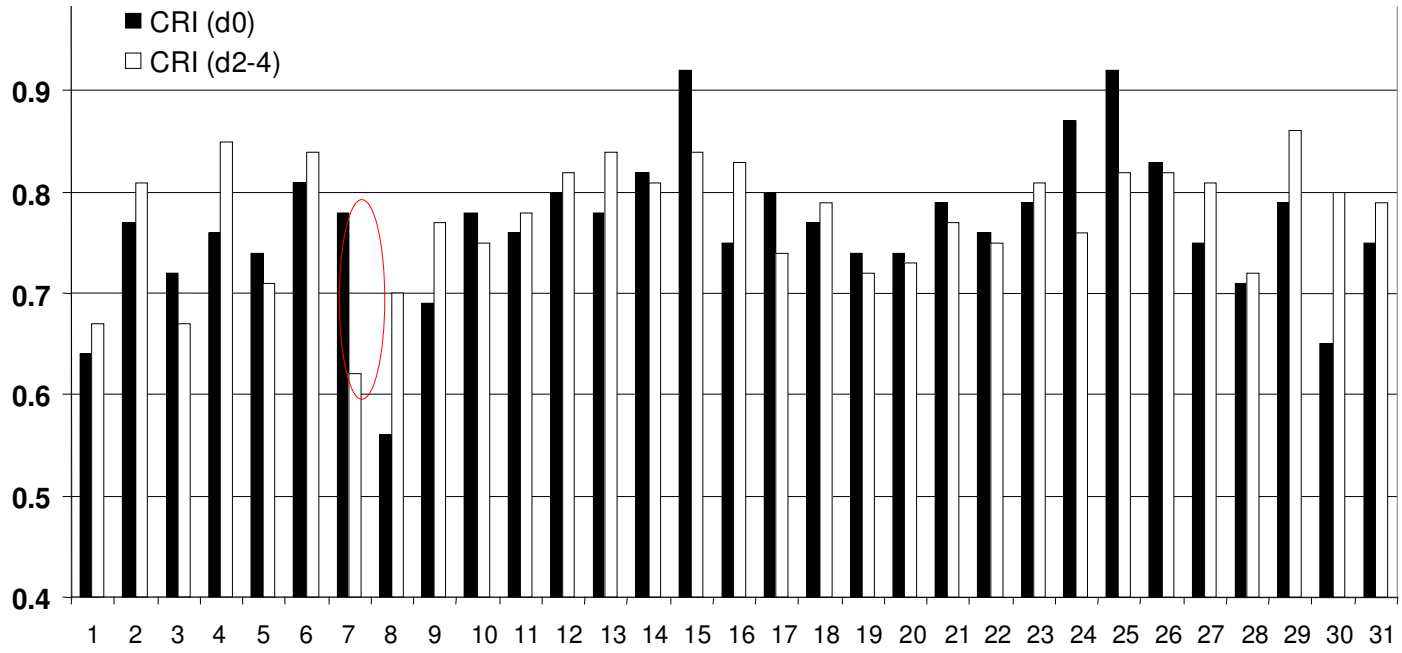

Figure 3. Cerebral resistance index (CRI) at admittance (d0) and after fever release (d2-4: day 2 to 4). The circles show an example of major drops in CRI.

DISCUSSION

Episodes of limited duration fever during pregnancy were not found to markedly alter placental (uterine and umbilical) or cerebral circulation to such an extent as to induce abnormal blood flow redistribution (C/U decrease >20%), as has been observed in cases of hypoxia.

Nevertheless, in at least half of the pregnancies observed in this study, maternal fever was associated with decreased uterine, umbilical, and cerebral flow

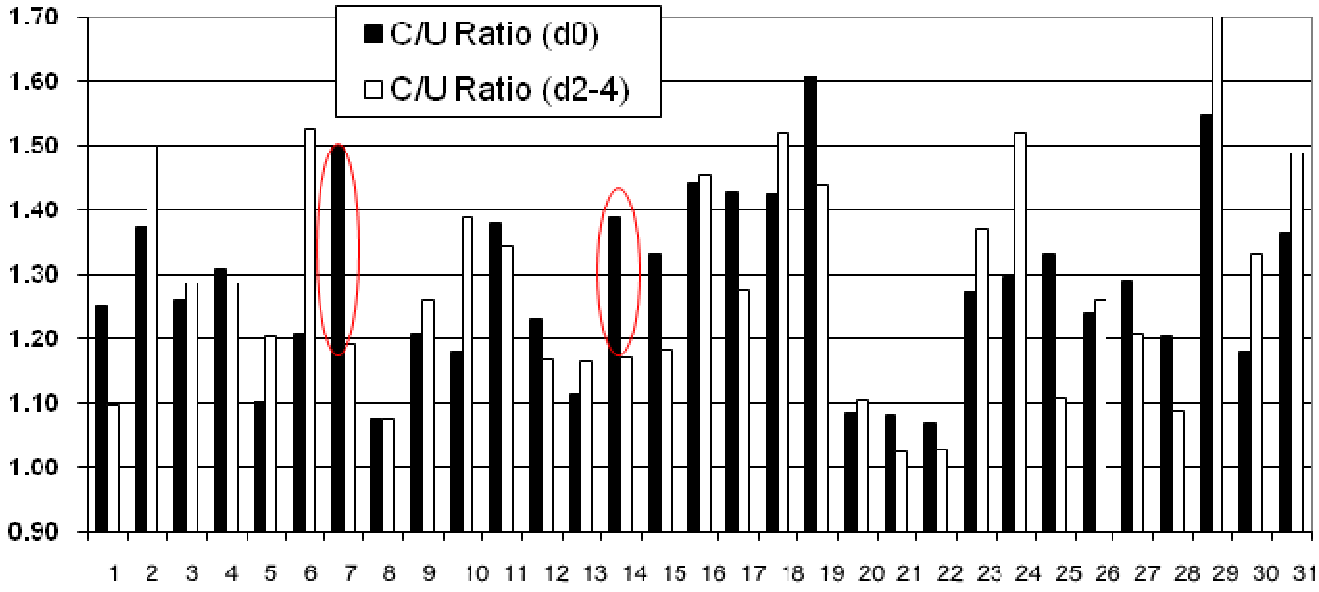

Figure 4. Cerebral-umbilical resistance ratio (C/U ratio) at admittance (d0) and after fever release (d2-4: day 2 to 4). The dotted line is the cut off limit for C/U. Below 1.1: It is considered that there is a fetal flow redistribution towards the brain in response to PO2 decrease. C/U below 1 means significant redistribution, significant hypoxia. The circles show an example of the major drops in C/U which means flow redistribution in favour of the brain but in this study C/U never reached the hypoxic zone (<1).

resistance indices, suggesting that the blood flow volume in these vessels were increased. Moreover, the decreases measured in C/U flow resistance ratio are indicative of a mild, but significant, redistribution of blood flow toward the foetal brain.

This blood flow redistribution pattern was similar to what has been observed in people suffering from malaria, or anaemia-induced hypoxia, but of much lower amplitude. In fact, the lowest C/U value at both day 0 and day 2-4 remained inside the “normal range” whilst in the case of Malaria, PIH or maternal anaemia, the lowest C/U value was significantly below normal ranges (<1.1) and associated with fetal complications at delivery (Arbeille et al., 2002, 2005; Carles et al., 2003).

During a malaria crisis, drop in C/U ratio can last from 3 or 4 days up to 10 to 15 days, depending on the duration of the crisis. It is the cumulative decrease in the C/U index over the time-course of the crisis which is considered the primary indicator of a deficit in O_2 delivery for the fetus, and thus associated with higher incidences of abnormal fetal heart rates at the end of pregnancy (Arbeille et al., 2002, 2005). Also, in the case of significant maternal anemia, there has been observed sustained reductions in C/U ratio, far below normal ranges (~1.1), until haemoglobin levels fully recover. Similar to cases of maternal malaria, these decreases sustained over several days were associated with abnormal fetal heart rates at the time of delivery. In case of malaria, reduction in oxygen transfer to the fetus was related to placenta lesion while in the case of anemia, it was related to reduction in maternal oxygen carrier but the fetal response was similar.

As the C/U values remained above 1 (the cut off limit of hypoxia) in this study, we may conclude that there was no significant hypoxia induced by the maternal fever, despite observing mild brain vasodilation which could not be considered immediately dangerous for the fetus. Nevertheless, because the fetal brain vessels were already mildly vasodilated, their capacity to vasodilate more will be reduced and any additional vasodilation required to counteract an episode of hypoxia may not be available (Suzuki et al., 2000).

Animal studies have reported an increase in uterine flow observed with elevations in maternal or fetal core temperature, and suggest that there is a perfusion-dependent transfer of heat from the fetus to the mother through the uterine circulation (Walker et al., 1995).

In fact, the present study has found that in the 66% of pregnancies observed, an increase in uterine flow via maternal hyperthermia that should be consistent with increased prostaglandin production, on both the fetal and maternal side, as observed during induced hyperthermia in animals (Andrianikis et al., 1989, 1994). Unfortunately, this hypothesis can not explain the responses observed in the remaining fever cases in which vascular resistance tended to increase in either the uterine or fetal areas. Nevertheless, the schedule of blood flow measurement on day 0 and 2- 4 was not taken on the basis of hemodynamic changes, but on the basis of clinical observation. Thus, if the hyperthermia and subsequent alterations in fetal blood flow had reduced during the night preceding the last measures, then the day of last measurements should have corresponded to a hemodynamic state already restored.

Also, elevations in maternal core temperature should trigger an increase in maternal heart rate such that, together with the decrease in vascular resistance, would increase cardiac output and ultimately contribute to an increase in the uterine blood flow. The higher rate of early uterine contraction and premature delivery observed with a decreased C/U index may be in direct relation to circulating vasoactive hormones (prostaglandin) produced during an episode of maternal hyperthermia.

Nevertheless, the relationship between maternal fever and uterine contraction has not been strongly proved yet. A study on baboon found a relationship (Morishima et al., 1975) while a second one in human did not found such relationship (Millar et al., 2003).

Conclusion

Contrary to malaria, the common infectious agent considered in the present study (Dengue, influenza, bronchitis, pyelonephritis) did not alter placental function nor induced fetal hypoxia. Maternal fever was associated to a mild cardiovascular response (increase uterine, umbilical or cerebral flow) probably triggered by the increase in core temperature.

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