Consequences of reduced umbilical and increased fœtal cerebral flow during malaria crisis on fœtal behaviour

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SUMMARY

The objectives of this study were (a) to evaluate the sensitivity and specificity of fœtal Doppler indices for the prediction of abnormal fœtal heart rate (aFHR) at delivery after malaria crisis and (b) to test Doppler parameters against crisis duration for predicting aFHR. Every day during the malaria crisis, the umbilical and cerebral vascular resistance indices were measured by Doppler. These indices allowed evaluation of the amplitude of the fœtal flow redistribution induced by malaria (C/U = cerebral resistance/umbilical resistance ratio), the duration of the flow redistribution period and the hypoxic index (mean %C/U change × crisis duration). It was found that the mean duration of the flow redistribution period was: 7 ± 2 days, mean C/U change −7% ± 4, hypoxic index −56 ± 37, prematures 35%, and aFHR 17%. An hypoxic index >150 predicted occurrence of aFHR with high sensitivity and specificity (100%/91%). The highest fœtal flow disturbance (max %C/U) and the duration of the period with flow disturbance (>7 days) predicted aFHR at delivery with a sensitivity of 10% and 40% and a specificity of 77% and 78%. It was concluded that the hypoxic index was more predictive of aFHR at delivery than the amplitude or the duration (i.e. crisis duration) of the fœtal flow redistribution.

Key words: malaria, fœtus, Doppler, hypoxia.

INTRODUCTION

Malaria transforms a normal pregnancy into a pathological pregnancy. The placenta acts as a filter by retaining the *Plasmodium falciparum*-parasitized red cell which causes a deterioration of the placenta consisting of degeneration of the chorionic villi, formation of deposits of fibrin and malarial pigment, thickening of the basement membrane, and accumulation of macrophages in the intervillous space (Galbraith *et al.* 1980; Walter, 1981; Gazin *et al.* 1994). The immune changes induced by pregnancy render the pregnant woman more vulnerable to malaria (Menendez, 1995). Pregnancy causes a reduction in overall immunity, and a reduction in acquired antimalarial immunity (cellular and humoral), particularly in the primipara. This change in immune status causes latent malaria to emerge and explains the serious forms. Malaria is more frequent and more serious during pregnancy, especially in primiparas (Menendez, 1995). In early pregnancy, malaria can be associated with abortion or fœtal death. Towards the end of gestation, malaria associated with premature birth and growth retardation can increase the risk of cerebral lesions of hypoxic origin (Greenwood *et al.* 1992; Morgan, 1994; Menendez, 1995).

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These 2 consequences could be related to acute or chronic placental insufficiency and fœtal hypoxia. Fœtal pO2 was not measured during malaria crisis, but fœtal Doppler can be used to detect any fœtal pO2 changes by measuring fœtal flow redistribution (Arbeille, 1991). Doppler examination of the fœtal blood vessels is widely used to confirm the existence of hæmodynamic abnormalities at the placental level accompanying intra-uterine growth restriction, and to evaluate the hæmodynamic response to hypoxia. Many studies have shown the usefulness of the umbilical and cerebral resistance indices in the detection of intra-uterine growth restriction and hypoxia (Trudinger, Giles & Cook, 1985; Brar & Platt, 1988; Maulik, Yarlagadda & Nathanielsz, 1989; Adamson *et al.* 1990; Fleischer, Schulmann & Farmakides, 1995).

The objectives of this study were (a) to evaluate the sensitivity and specificity of fœtal Doppler indices for the prediction of abnormal fœtal heart rate (aFHR) at delivery after a malaria crisis and (b) to test Doppler parameters against crisis duration for predicting aFHR.

MATERIALS AND METHODS

Population

The study, designed as a prospective and observational one, was carried out in the Obstetrics Department of a government hospital in French Guiana. The study group consisted of 23 pregnancies

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all complicated by a malaria infection (*Plasmodium falciparum*).

Protocol

The hospital at Saint Laurent du Maroni (French Guiana) receives a substantial number of pregnancies complicated by malaria. These gestations originate from areas distributed along the Maroni River. At the first clinical signs of malaria infection, the gravidas were treated and transferred to the Obstetrics Department at the hospital. Admission of the cases and the monitoring of the growth and fœtal circulation by ultrasound and Doppler were carried out according to a well-defined protocol: Doppler investigation consisted of uterine, umbilical and cerebral arteries recording at admission, then daily recording of cerebral and umbilical arteries during the crisis. Echography for examination of the placenta and amniotic fluid volume, and fœtal biometry were performed every 2 days. This protocol started at admission and was continued until the end of the crisis (remission of the clinical, haematological, and hæmodynamic signs). The diagnosis of malaria was based on the presence of fever, and the detection of parasites in the maternal blood. The maternal blood analysis was performed every day during the crisis, and the treatment was stopped when no more parasites were seen.

After leaving the hospital, each gravida was seen as regularly as possible and at each visit underwent a complete ultrasound-Doppler examination. Following delivery, the perinatal data were collected.

Fœtal hæmodynamic data

The uterine vascular resistance indices were measured at admission only. The distribution of the fœtal cardiac output between the placental and cerebral regions was evaluated using the C/U ratio, which is the ratio between the cerebral and umbilical resistance indices (Arbeille, 1991). In normal pregnancies the umbilical resistances are lower than the cerebral one which means that the cardiac output is preferably oriented towards the placenta area and the C/U ratio is always greater than 1·1. Most of the time, placenta insufficiency (maternal hypertension, infection, or drug abuse) is associated with an increase in the umbilical (placental) vascular resistance, and a decrease in the cerebral resistance due to a cerebral vasodilation in response to hypoxia. In these cases the C/U ratio decreases proportionally with the fœtal partial pressure of oxygen [pO2] and its absolute minimum value is proportional to the lowest level of the fœtal pO2 (Bonnin, Guyot & Blot, 1992; Arbeille *et al*. 1995). In addition, the C/U ratio is not dependent on the fœtal heart rate (as are the other Doppler indices), and has a cut-off limit between the normal and pathological zones which is constant throughout gestation and equal to 1·1 at least from 25 to 40 weeks (Arbeille, 1991).

The variation in the C/U ratio was expressed as a percentage compared to the normal value measured at the end of the crisis. The hypoxic index (HI) was calculated from the mean variation in the C/U ratio (%C/U) during the crisis and the duration of the crisis (in days): hypoxic index = (mean %C/U change) × (crisis duration). The mean variation of the C/U ratio represents the mean pO2 decrease (Bonnin *et al*. 1992; Arbeille *et al*. 1995), and thus the area between the C/U ratio curve and the time axis represents the cumulated deficit in pO2 during the crisis. The hypoxic index therefore combines information on the amplitude of the flow redistribution towards the brain (i.e. pO2 decrease), and the duration of exposure to hypoxia (Arbeille, 1991). The cut-off value of 150 for the hypoxic index was determined during a retrospective study on pregnancies complicated by hypertension (personal unpublished data).

At each daily Doppler examination we first measured the umbilical and cerebral resistances, and then C/U and the HI were calculated. Uterine vascular resistance was only measured at admission of the gravida. Doppler examinations were performed by the 2 obstetricians in charge of the pregnancies, using a Hitachi EUB 44.

Perinatal data

The Doppler data were compared with the fœtal and maternal perinatal data: fœtal heart rate monitoring at delivery (FHR), gestational age at delivery and type of delivery, Apgar score at 5 min and fœtal weight after delivery, maternal parasitæmia (grade 1–5), parity of the gravida, date of the onset of the crisis, crisis duration, and number of days before treatment. The FHR was considered as abnormal in case of low modulation, or late decelerations. FHR traces were evaluated blindly by the 2 obstetricians. The Apgar score at 5 min was considered as pathological when lower than 7. The parasitæmia grade represents the concentration of parasitized red blood cells per mm^3 of maternal blood (grade 1: 0–1000; grade 2: 1000–2500; grade 3: 2500–10 000; grade 4: 10 000–50 000; grade 5: >50 000). Normal delivery was defined as at-term delivery, without any signs of fœtal distress or maternal complication. Caesarean section was performed only because of fœtal distress.

Data processing

The Doppler parameters were averaged over 10 cardiac cycles. The Doppler parameters were compared with the fœtal and maternal perinatal data. Normal or abnormal Doppler data were compared with the occurrence of abnormal fœtal heart rate (aFHR), prematurity, caesarean section, abnormal Apgar score at 1 min, using a chi-square test. The

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Table 1. Maternal and fœtal parameters

Maternal and fœtal parameters	All crisis
Age (years)	24±2·1
Parity	2·7±2
Crisis gestational age	31·3±4
Crisis duration (days)	6·1±2
Days before treatment	2·61±1·44
Parasitæmia	2·78±1·2
Delivery (weeks)	37±2
Caesarean section	4 (17%)
Abnormal FHR	4 (17%)
Apgar <10	7 (30%)
Apgar <7	4 (17%)
Premature	8 (35%)
IUGR (<10c)	4 (17%)

numerical values of the Doppler parameters were compared with the duration of the crisis (days), the grade of parasitæmia (1–5), the date of the crisis, the number of days before treatment using a Mann–Whitney non-parametric test. The limit for significance was set at $P=0{\cdot}05$. The ability of the Doppler parameters (minimal C/U, HI) and the crisis duration to predict the occurrence of aFHR was expressed in terms of sensitivity, specificity, positive and negative predictive values.

RESULTS

The duration of the study was 1 year. Forty pregnancies complicated by malaria were investigated, but the complete Doppler and clinical data needed for the study were collected in only 23 of them. The other pregnancies, assessed by Doppler during their stay at the hospital, returned to their villages, and their deliveries could not be monitored.

Perinatal data are presented in Table 1. The fœtal umbilical and cerebral Doppler traces were successfully recorded at each daily Doppler session. Doppler data at admission, and percentage changes of these parameters during the crisis are presented in Table 2 and Figs 1 and 2. Sensitivity, specificity, positive predictive and negative predictive values of the lowest C/U absolute value (abnormal when <1·1), crisis duration (>7 days), HI (>150) for predicting abnormal fœtal heart rate at delivery (aFHR) are presented in Table 3 and Fig. 3. Figure 1 shows the mean variations (in percent) of umbilical and cerebral resistance and C/U ratio. There was no significant correlation between the amplitude of the redistribution of the fœtal flows (mean %C/U ratio variations), or the HI, and the following parameters: the grade of parasitæmia, the parity of the pregnancy, the gestational age at the time of the crisis, the number of days before treatment, the gestational age at delivery, the mode of delivery, the time between crisis and delivery, the fœtal weight at birth.

The HI predicted abnormal FHR at delivery with a good sensitivity and specificity. Conversely, the lowest C/U value and crisis duration (days) did not predict aFHR with good sensitivity or specificity (Table 3).

Table 2. Doppler data at admission and during the crisis

	All crisis
Doppler at admission	
UT RI at admission	0·44±0·09
C/U at admission	1·19±0·14
URI at admission	0·64±0·05
CRI at admission	0·75±0·07
Doppler during crisis	
Lowest C/U in crisis	1·09±0·13
Max %C/U decrease	−16±7·5
Days with flow redistribution (%C/U<1·1)	7±2
Mean %C/U change during the crisis	−7±4
HI (Hypoxic index)	−56±37

DISCUSSION

The fœtal Doppler performed during the crisis showed that the malarial infection induced a range of transient hæmodynamic changes at the placental and cerebral level. In all cases, there was an increase of the umbilical resistances which is consistent with the degradation of the vascular bed reported by previous studies (Walter, 1981; Greenwood *et al*. 1992; Morgan, 1994). Relatively high uterine resistance indices were also found but only in 34% of the pregnancies, which is in agreement with previous studies which reported the existence of placental lesion in 50% of cases (Galbraith *et al*. 1980; Walter, 1981; Greenwood *et al*. 1992; Gazin *et al*. 1994; Morgan, 1994; Menendez, 1995). The uterine resistance at admission was not correlated with either the parasitæmia or the fœtal cerebral and umbilical hæmodynamic changes during the crisis, nor with the crisis duration.

Umbilical and cerebral resistance became abnormal during the crisis in 17%, 39% of the cases respectively, but C/U ratio was abnormal in 48% of the cases which suggests that at least 48% of the fœtuses were hypoxic. Umbilical resistance increased, and the cerebral resistance decreased more than 10% from normal in 14 out of the 23 cases (60%) which confirmed that more than half of the fœtuses were submitted to significant hæmodynamic changes. On the other hand there was no correlation between the crisis duration and the increase in placental resistance or decrease in cerebral resistance.

As a response to the deterioration of the foeto-maternal exchanges, a reduction in the cerebral vascular resistance by vasodilation was observed, which resulted in an increase in the cerebral perfusion and thus of oxygen supply. Previous studies on

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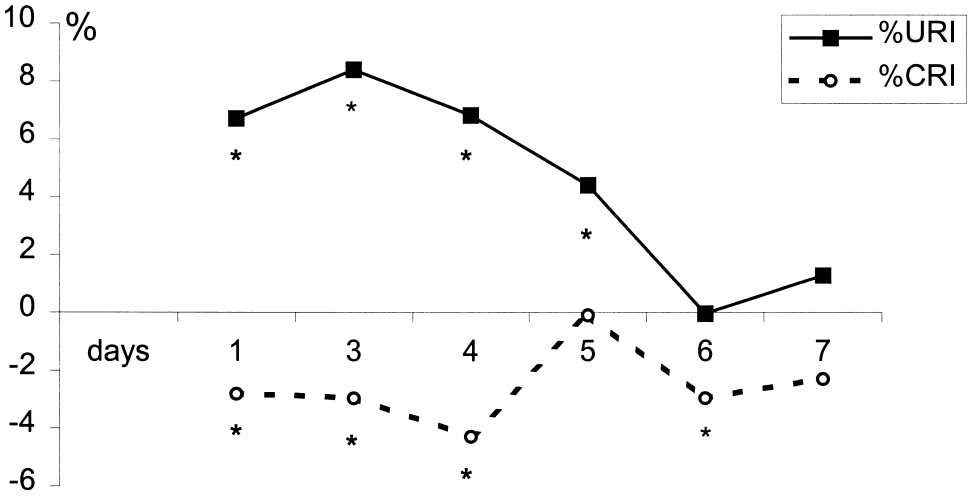

Fig. 1. Mean variations of umbilical (URI) and cerebral (CRI) resistance index during the malaria crisis (*$P<0{\cdot}05$).

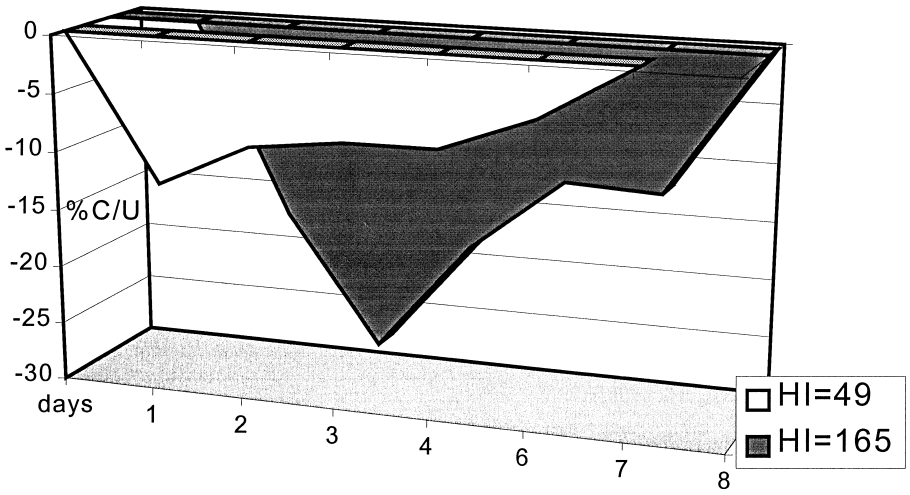

Fig. 2. Percentage change in Cerebral/Umbilical ratio (%C/U) during malaria crisis. The area between the %C/U curve and the time axis (days) represents the hypoxic index (HI) value. As the C/U ratio changes proportionately to the fœtal pO2, this area is considered to represent the cumulated deficit in pO2 over the crisis. The smallest area (white) represents an HI value of 49 (HI < 150) which is associated with normal FHR at delivery. The largest area (grey) represents a HI value of 165 (HI > 150) which is associated with abnormal FHR at delivery.

pregnancies complicated by hypertension showed that the C/U ratio, which measures the flow redistribution, varies proportionally to the fœtal pO2 (Arbeille *et al*. 1995). As it decreases during a malaria crisis one can suggest that the fœtal pO2 reduces during the crisis. The mean C/U value ($1{\cdot}19 \pm 0{\cdot}14$) at admission was close to the cut-off limit (1·1), which suggests that the level of hypoxia was rather low for the majority of the fœtuses whereas abnormal values as low as 0·9 were found in 6 out of the 23 cases (26%).

The C/U ratio has been tested on hypertensive pregnancies, on pregnancies with idiopathic growth restriction, and on twin pregnancies (Wladimiroff, Wijngaard & Degani, 1987; Arbeille, 1991; Bonnin *et al*. 1992) and in all cases the sensitivity of this parameter (abnormal when <1·1) for the detection of intra-uterine growth restriction was similar (sensitivity 85%, specificity 98%). This parameter has subsequently been tested as a predictor of the occurrence of acute fœtal distress at birth and of neonatal complications. In this application the sensitivity was 90% for the C/U ratio, 78% for the cerebral index, and 80% for the umbilical index (Gramellini *et al*. 1992). The present study confirms the superiority of the C/U ratio compared to cerebral or umbilical indices, for detecting fœtal vascular abnormalities associated with flow redistribution in relation to placental insufficiency (Fignon *et al*. 1996; Arbeille *et al*. 1997).

The minimum C/U ratio was used to predict the occurrence of FHR abnormalities at the end of gestation, but its sensitivity (10%) and specificity (77%) was not very high.

Another factor for evaluating hypoxia is the mean C/U ratio variation during the crisis. This variation,

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Table 3. Sensitivity, specificity, positive and negative predictive value for HI (hypoxic index <150 or >150), lowest C/U during the crisis (proportionate to the lowest level pO2; abnormal <1·1 or normal >1·1), crisis duration (in days) in predicting abnormal fœtal heart rate (aFHR)

Parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
HI>150 *vs* aFHR	100	91	50	100
C/U<1·1 *vs* aFHR	10	77	25	53
Crisis >7 days *vs* aFHR	40	78	33	82

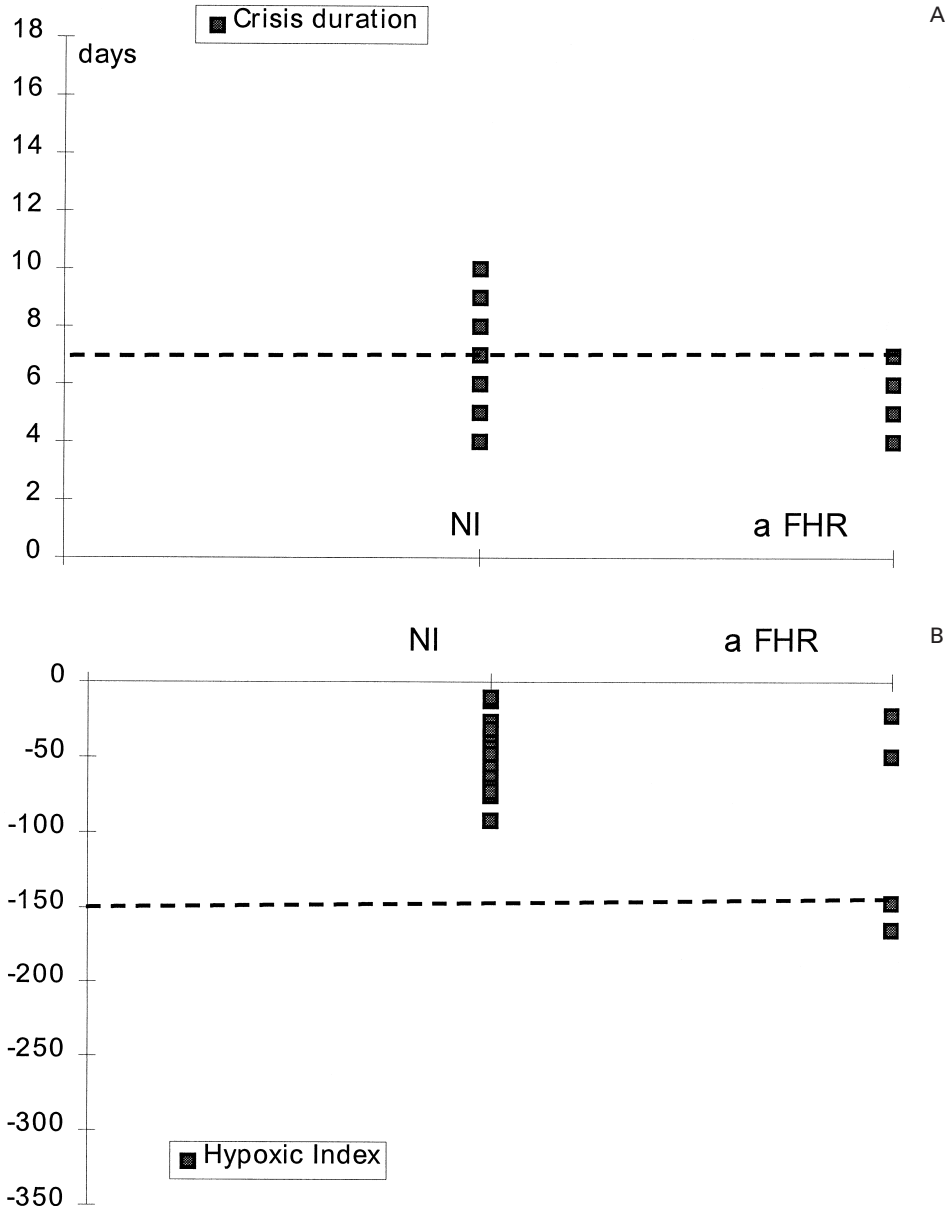

Fig. 3. (A) Abnormal fœtal heart rate (aFHR) versus crisis duration (>7 days). There is no correlation at all between the crisis duration higher than 7 days and the occurrence of abnormal FHR. (B) Abnormal fœtal heart rate (aFHR) versus hypoxic index >150. Half of the cases with aFHR are identified by an HI>150, whereas all cases without aFHR corresponded to an HI<150.

expressed as a percentage of the normal value at the end of the crisis, measures the mean flow redistribution amplitude and thus the mean drop in pO2 (Arbeille *et al.* 1995). The mean C/U variation during the crisis was 8%±8 but this parameter predicted occurrence of aFHR with rather poor sensitivity and specificity (10% and 77%). Moreover, there was no direct relation between the amplitude

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of the C/U ratio variation and the following data: grade of parasitæmia, parity, gestational age at crisis, date and mode of delivery, fœtal weight.

The duration of the flow redistribution period (i.e. crisis) was partially correlated with aFHR at delivery but the sensitivity and specificity of the crisis duration (>7 days) for predicting aFHR was rather modest (40% and 78%). One may notice that the distribution range of the flow redistribution period (7 ± 2 days) was rather large.

The hypoxic index, combining both the amplitude of the C/U ratio variation (i.e. fall in pO2) and the crisis duration (period with flow redistribution i.e. with C/U <1·1), has thus been calculated and tested as a factor for predicting aFHR at delivery. The hypoxic index (% change of C/U ratio × crisis duration in days) is thought to represent the cumulated lack of pO2 [e.g. HI = 49 corresponds to 7 days of −7% pO2 reduction (7×7), or 3 days of −16·3% pO2 reduction ($3 \times 16{\cdot}3$), HI = 165 corresponds to 11 days of −15% pO2 reduction (11×15), or to 5 days of 33% pO2 reduction (5×33)]. Only crises of long duration and with substantial C/U decrease (flow redistribution) can provide an HI > 150. The limit of 150 was found retrospectively on populations of pregnancies complicated by hypertension (personal unpublished data) and tested in the present study. In fact, an HI of higher than 150 was found to be the best parameter for predicting the occurrence of aFHR (sensitivity 100%, specificity 91%). Lastly, even though the short crises were less frequently associated with aFHR than long crises, the duration of the crisis was not sufficient to predict aFHR at delivery. Only the HI was found to be a good predictor of such functional abnormality.

There was no severe fœtal distress at delivery and no sign of neurological handicap after delivery, which supports the hypothesis that consequences of the supposed transient hypoxia induced by malaria are limited to functional disturbances like aFHR. On the other hand, the transient hypoxia had a limited effect on the fœtal growth (17% of the cases between 5 and 10 centile). Moreover, the duration of the crisis was not correlated with the degree of growth restriction. This observation is in agreement with the fact that the crisis took place several weeks before delivery, a period of time during which the fœtus could have a normal growth, even if part of the fœtal physiological systems (autonomic nervous system) did not recover in between.

The gestational age at which the crisis occurred was not correlated with either the crisis duration nor with the rate of aFHR or the amplitude of the fœtal flow redistribution. This observation suggests that the capacity of the fœtus to respond to acute hypoxia and the vulnerability of the fœtal physiological functions were similar between 27 and 35 weeks.

In the population studied, malaria affected multiparas and primiparas equally, which tends to show that successive pregnancies do not induce any protection against malaria. Moreover, the crises with short-duration flow redistribution were not necessarily in those patients who were treated before 3 days of crisis.

Recent observations tend to show that there is a progressive decrease in the fœtal hæmodynamic consequences induced by malaria. It seems that if any acquired immunity or protection has already developed with time it is more related to maternal immunity than to repeated pregnancy-induced immunity. Malaria appeared in French Guyana around 1990, at that time there were no sanitary countermeasures against malaria and the first malaria crisis sometimes occurred during pregnancy. The consequences for the fœtus were dramatic, including abortion, *in utero* fœtal death, severe oligoamnios … Presently there are still malaria infections during pregnancy but women have already been exposed to malaria several times during their pregnancies. This could explain that the consequences for the fœtuses are not as severe as before and that fœtuses are similarly affected during primiparas and multiparas.

In the present study the absence of large and extended flow redistribution as measured by cerebral and umbilical Doppler, the reduced fœtal vascular disturbance at admission (mean $16\% \pm 7$ during 7 ± 2 days), and the rather low rate of aFHR (17%) suggest that the fœtus is not severely affected by the maternal malaria infection.

The maternal and clinical data do not allow evaluation of the consequences of malaria on the fœtus, whereas the fœtal Doppler detects the flow redistribution triggered by the hypoxia and predicts the occurrence of aFHR at delivery. In the case of first exposure to malaria the fœtal Doppler may detect severe hypoxia and introduce a new parameter in the obstetrical decision making. Conversely, in the case of a patient already infected by malaria the fœtal Doppler will probably reveal minor hæmodynamic changes and lead to the assumption that there is no real risk for the fœtus.

In conclusion, we have shown that close monitoring of the fœtal circulation by Doppler during a malaria crisis allows measurement of the duration and the amplitude of the fœtal vascular disturbance induced by malaria. The consequences of this pathology for fœtal development and outcome can thus be predicted.

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