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# Association of non-reassuring fetal heart rate and fetal acidosis with placental histopathology

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ABSTRACT

*Objective:* To investigate the association between different placental lesions and non-reassuring fetal heart rate (NRFHR) pattern and fetal acidosis in labor.
*Study design:* Placentas from 213 women who underwent cesarean section because of NRFHR with or without fetal acidosis (pH < 7.2) were classified by histopathologic findings: consistent with maternal circulation abnormalities i.e., namely, marginal or retroplacental hemorrhage (M0), maternal underperfusion, vascular (M1) or villous changes (M2), and those consistent with fetal thrombo-occlusive disease due to vascular (F1) or villous (F2) changes. Lesions were also analyzed by maternal (MIR) or fetal (FIR) origin of inflammatory responses.
*Results:* Cord blood pH was normal in 169 neonates (7.29 ± 0.04; control group) and <7.2 in 44 (7.10 ± 0.07; study group). The study group had higher rates of histologic chorioamnionitis; MIR was detected in 34.1% compared to17.8% of controls ($p = 0.018$), and FIR, in 18.2% compared to 6.5% ($p = 0.016$). Neonates in the study group had lower Apgar scores and longer hospitalization.
*Conclusions:* Placental MIR and FIR are associated with cord blood acidosis in neonates delivered by cesarean section for NRFHR tracings in labor.

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## 1. Introduction

Non-reassuring fetal heart rate (NRFHR) patterns during labor, are considered to be an indication of fetal hypoxia and acidosis, which can sometimes lead to neonatal morbidity and mortality [1]. However, only a few studies have investigated the role of pathologic placental processes in the development of NRFHR, especially in fetuses that acquired acidosis (manifested as low cord blood pH) with contradictory results. Salafia et al. [2,3] reported an association between abnormal FHR patterns (variable and late decelerations) and acute inflammation of the placenta. By contrast, Moberg et al. [4] observed an increased prevalence of FHR tracings consistent with umbilical cord compression in women with preterm premature rupture of the membranes, with no increase in placental findings suggestive of chorioamnionitis. Others [5] found that abnormal FHR tracings are an imprecise predictor of fetal inflammatory response and neonatal sepsis. Although these studies correlated FHR patterns to placental findings, they did not analyze cord blood pH data. Additional studies, approaching the issue from a different perspective, investigated the relationship of cord blood acidemia to adverse neonatal outcome, but they did not include a placental evaluation [6] or an analysis of the FHR pattern [7] and they were based on term and preterm deliveries [5].

The Society for Pediatric Pathology recently recategorized placental lesions into those consistent with changes in the maternal vascular circulation (maternal underperfusion) and those consistent with changes in the fetal vascular supply (thrombo-occlusive disease) [8]. This has made it easier to determine the role of the placenta in the development of NRFHR and acidosis during labor. The aim of this study was to investigate different placental lesions by maternal- or fetal-origin in pregnancies complicated by NRFHR with or without fetal acidosis.

## 2. Material and methods

### 2.1. Patients and procedure

We reviewed the medical records of all patients who underwent emergent cesarean section (CS) because of persistent NRFHR at the Department of Obstetrics and Gynecology, Edith Wolfson Medical Center, Holon, Israel, from January 2007 to December 2009.Additional inclusion criteria were presentation in active labor at gestational age ≥37 weeks. Gestational age was confirmed by first-trimester

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ultrasonography. Active labor was defined as regular painful uterine contractions and cervical dilatation of >2 cm with or without rupture of the membranes (ROM). Patients with ROM and prolonged latency period (>18 h) were treated with antibiotics, according to the departmental protocol [9]. The latency period was defined as the time elapsed (in hours) from onset of membrane rupture or amniotomy to delivery. All patients were continuously monitored by an electronic fetal monitor. The decision to perform CS was made by the senior attending physician of the department. The diagnosis of NRFHR (recurrent late and variable decelerations, bradycardia, sinusoidal pattern and loss of variability) was made on the basis of FHR tracing equivalent to category III FHR tracings, according to the recent guidelines of The American College of Obstetrics and Gynecology [1] and a failure to respond to intrauterine resuscitation such as change in maternal position, provision of maternal oxygen, discontinuation oxytocin infusion, treatment maternal hypotension and treatment with tocolysis in cases of uterine tachsystole. During surgery, immediately after delivery and before placental removal, blood samples from the umbilical vessels were sent for blood gas analysis, including pH and base excess. Blood was analyzed within 30 min of withdrawal (Blood Gas Analyzer, Cobas 221, Roche Diagnostics, USA).

For purposes of the study, the study population was divided into two groups by the umbilical cord pH $\geq$ 7.2 (control group) or <7.2 (study group) [10]. Approval for the study was obtained from the Local Ethics Committee.

### 2.2. Data collection

The clinical and histopathologic data for the present study were collected from the patients' medical files as follows: age, gravidity, and parity; cigarette smoking (number per day); known chronic diseases such as epilepsy, asthma, hypo/hyperthyroidism; chronic pharmacotherapy, defined as medical treatment taken by the patient during the whole pregnancy, except vitamins or iron supplements; maternal body mass index (BMI), calculated as the pre-pregnancy weight in kilograms divided by height in meters squared. At birth, all neonates were examined by a pediatrician. Birth weight was determined and the specific weight percentile was calculated using the updated Israeli growth charts [11]. The following information was collected from the neonatal medical records: Apgar scores, length of hospitalization, sepsis (defined as positive blood or cerebrospinal fluid culture), respiratory distress syndrome (defined as clinical signs of respiratory distress warranting treatment with oxygen, and continuous nasal pressure or mechanical ventilation, with typical radiographic appearance), need for mechanical ventilation, periventricular leukomalacia, intraventricular hemorrhage, and diagnosis of hypoxic ischemic encephalopathy or seizures. Cranial ultrasound was performed in neonates in whom an abnormality was detected on physical examination.

In order to eliminate confounding factors that may have affected placental findings, patients with pregestational or gestational diabetes A2 (GDMA2) were excluded from the study, as were patients with thrombophilia, chronic hypertension, preeclampsia, intrapartum fever, multiple pregnancies, pregnancies complicated by neonatal chromosomal or structural anomalies or proven intrauterine infection, and neonates with birth weights below the 10th percentile.

### 2.3. Placental examination

Placental pathology examinations were performed using a standard protocol, described by us in a previous study [12] using the criteria originally proposed by the Society for Pediatric Pathology (8). Placental weight, in formalin fixation, was determined 24 h after delivery, and the percentile was determined according to specific placental weight charts [13]. The fetoplacental weight ratio was calculated as the ratio between the fetal birth weight and the placental weight. Each placenta was fixed in formalin, and at least 5 tissue samples of placental tissue were embedded in paraffin blocks for microscopic assessment. One free membrane roll (chorion and amnion with attached decidua capsularis), two section of umbilical cord, and four full-thickness disc samples were taken as follows: one block each at the cord insertion from central tissue and at the margin, and one or more blocks from tissue that appeared abnormal on gross examination. All examinations were done by a single pathologist (L.S.), who was not blinded to the patients' clinical background but was unaware of the infants' clinical outcome or cord pH.

#### 2.3.1. Placental vascular and villous lesions

The placental lesions evaluated as part of this study were classified into two main groups, as suggested by the Society for Pediatric Pathology (8): lesions of maternal-origin (M) (consistent with maternal circulation abnormalities) and lesions of fetal-origin (F) (consistent with thrombo-occlusive disease). Lesions of maternal-origin were categorized as marginal and retroplacental hemorrhages (M0), vascular underperfusion changes (acute atherosis and mural hypertrophy) (M1), and villous underperfusion changes (increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, and villous infarcts) (M2). Lesions of fetal-origin (F) were categorized as vascular lesions (thrombosis of the chorionic plate and stem villous vessels) (F1) and villous changes (avascular villi) (F2).

#### 2.3.2. Placental inflammatory lesions

Placental findings consistent with chorioamnionitis were defined by the presence of an inflammatory neutrophil infiltrate at two or more sites on the chorionic plate and extraplacental membrane. The maternal inflammatory response (MIR) was divided into three stages; stage 1 – early, acute subchorionitis, characterized by the presence of a few scattered neutrophils (5–10 per high-powered field) in the subchorionic space; stage 2 – intermediate acute chorioamnionitis, characterized by many neutrophils (11–30 per high-powered field) in the lower half of the chorionic plate; and stage 3 – late, severe chorioamnionitis, characterized by dense infiltrates of neutrophils (more than 30 per high-powered field) throughout the chorionic plate. The fetal inflammatory response (FIR) was also divided into 3 stages: stage 1 – early, umbilical phlebitis; stage 2 – intermediate, umbilical arteritis; and stage 3 – concentric umbilical perivasculitis ("necrotizing funisitis") [8].

Placental histologic examination also included the detection of meconium-stained membranes associated with columnar change in amniotic epithelium or the appearance of pigmented macrophages.

### 2.4. Statistical analysis

Data were analyzed with SPSS software, version 15.0. Continuous variables were calculated as mean ± SD or median and range, as appropriate. Categorical variables were calculated as rate (%). Continuous parameters were analyzed by Student *t*-test and categorical variables by chi-square test or by Fisher exact test, as appropriate. To determine the effect of the latency period on the placental findings, the presence or absence of the placental inflammatory changes was compared by Mann–Whitney test (because of the nonparametric distribution of the data). A $p$ value of <0.05 was considered statistically significant. Calculation of the required sample size indicated that a group of 40 subjects was sufficient to achieve 80% power and an alpha error of 0.05, to detect a difference of 40% in total MIR between a study group and a control group with a baseline rate of 25%, according to our own data. A multivariate logistic regression was performed with stepwise forward analysis for total MIR as dependent variable and maternal age, smoking, BMI, gestational age, latency time, birth weight, and placental weight as independent variables.

## 3. Results

A total of 213 patients who underwent CS due to NRFHR were included in the study: 169 (79.3%) with umbilical cord pH $\geq$ 7.2 (mean 7.29 ± 0.04; control group) and 44 (20.6%) with umbilical cord pH < 7.2 (mean 7.10 ± 0.07; study group).

The maternal characteristics are summarized in Table 1. There were no between-group differences in mean maternal age, nulliparity, BMI, weight gain during pregnancy or in the rate of cigarette smoking. Other maternal diseases were few, with no differences between the groups (results not shown). There were no between-group differences in, birth weight, and birth weight percentile, as expected by our exclusion of neonates with growth restriction.

The placental characteristics are summarized in Table 2. Mean placental weight was significantly lower in the study group ($p = 0.049$), as was the incidence of placental weight below the 10th percentile, adjusted for gestational age ($p = 0.007$). However,

**Table 1**
Maternal and delivery characteristics of patients who underwent cesarean section for non-reassuring fetal heart rate, by cord blood pH.

| | Control group cord pH $\geq$ 7.2 $n = 169$ | Study group cord pH < 7.2 $n = 44$ | *P* value |
|---|---|---|---|
| Maternal age (yrs) | 30.9 ± 5.6 | 30.1 ± 5.0 | 0.407 |
| Nulliparity (%) | 41.4% | 36.4% | 0.662 |
| BMI (kg/m$^2$) | 24.4 ± 5.0 | 23.7 ± 3.9 | 0.433 |
| Maternal weight gain (kg) | 14.8 ± 6.3 | 15.7 ± 6.1 | 0.544 |
| Smokers (%) | 11.8 | 13.6 | 0.745 |
| Gestational age at delivery (wks) | 39.8 ± 1.1 | 39.7 ± 1.0 | 0.339 |
| Latency (hr)[a] | 3.56 ± 7.5 | 4.90 ± 6.2 | 0.28 |
| Birth weight (gr) | 3257 ± 416 | 3175 ± 340 | 0.229 |
| Birth weight percentile (%) | 49.3 ± 27 | 45.8 ± 25 | 0.436 |

Continuous variables are presented as mean ± SD.
[a] Latency period was compared between the groups by using the Mann–Whitney test.

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