Placenta – The fetal lung in utero

Ph.D. Thesis

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1. Introduction

1.1. What is the topic?

Our focus is on intrauterine inflammation (IUI), with a special emphasis on the fetal inflammatory response (FIR) and its implications for neonatal outcomes. Additionally, it investigates the role of optimized respiratory management in the vulnerable periextubation period of preterm infants.

1.2. What is the problem to solve?

Despite the established link between FIR and adverse neonatal outcomes, FIR is still underutilized in neonatal risk stratification. Clinical practice rarely integrates detailed histopathological data, particularly the topographical extent of FIR.

Furthermore, while efforts are made to minimize mechanical ventilation (MV) in neonatal intensive care units (NICUs), the extubation failure rate remains high.

1.3. What is the importance of the topic?

FIR affects a substantial proportion of preterm births and is strongly associated with complications such as sepsis, intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD). Understanding its anatomical distribution may enhance the clinical utility of placental pathology.

Simultaneously, improving extubation practices could reduce reintubation rates and related complications. Together, these aspects offer pathways to refine neonatal care and advance personalized interventions.

1.4. What would be the impact of our research results?

Our aim is to reposition FIR from a static histological finding to a clinically actionable marker. To provide evidence for FIR's role in predicting outcomes and highlight the significance of its location.

Furthermore, we propose a targeted intervention - an additional pre-extubational caffeine dose - which could reduce extubation failure in high-risk neonates.

2. Objectives

2.1. Study I- The histologic fetal inflammatory response and neonatal outcomes: systematic review and meta-analysis

Maternal inflammatory response (MIR) is strongly associated with adverse neonatal outcomes, including sepsis, BPD, IVH, and long-term neurodevelopmental issues. In up to 70% of cases, MIR is accompanied by a FIR, but its additional impact remains debated. To clarify this, we conducted a systematic review and meta-analysis comparing neonatal outcomes in preterm infants with MIR alone versus MIR with FIR.

2.2. Study II- The route of intrauterine inflammation along the umbilical cord: a retrospective analysis of placental specimens from a 3-year cohort

The direction of IUI on the placenta-umbilical cord-fetus axis is unclear, as infections may start in the placenta, fetus, or occur randomly. The objective was to determine whether FIR shows a directional progression along the UC and the fetal vessels. This study also examined how these

histological findings correlated with maternal and neonatal outcomes.

2.3. Study III - The effect of an additional pre-extubational loading dose of caffeine citrate on mechanically ventilated preterm infants (NEOKOFF trial): Study protocol for a multicenter randomized clinical trial

Since the Caffeine for Apnea of Prematurity trial, caffeine has become a standard treatment in neonatal intensive care. However, there are still unanswered questions regarding ideal dosing and timing. To address this, we designed a clinical trial to evaluate whether a single additional loading dose of caffeine citrate given one hour before extubation improves extubation success. The study also aims to monitor the frequency and severity of potential side effects.

3. Methods

3.1. Study I- The histologic fetal inflammatory response and neonatal outcomes: systematic review and meta-analysis

The systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines to assess the association between the presence of FIR and neonatal outcomes in preterm infants. Studies were identified through a comprehensive search of multiple databases (MEDLINE, Embase, CENTRAL, and Scopus) and screened using predefined eligibility criteria. Subgroup analysis was conducted based on the definition of FIR used in each study and the mean gestational age. The QUIPS tool was used for determining the risk of bias. Primary outcomes were mortality, sepsis, necrotizing enterocolitis, and bronchopulmonary dysplasia.

3.2. Study II- The route of intrauterine inflammation along the umbilical cord: a retrospective analysis of placental specimens from a 3-year cohort

This retrospective study of a 3-year cohort analyzed placental and umbilical cord specimens from preterm deliveries to evaluate the topographical progression of histological inflammation. Histological examination was conducted according to the Amsterdam Placental Workshop Group Consensus Statement. MIR and FIR were separated. FIR was categorized by its anatomical location - such as chorionic plate, umbilical vessels, and Wharton's jelly - and severity. Clinical data were collected from electronic patient charts.

3.3. Study III - The effect of an additional pre-extubational loading dose of caffeine citrate on mechanically ventilated preterm infants (NEOKOFF trial): Study protocol for a multicenter randomized clinical trial

The NEOKOFF study is a prospective, randomized, open-label, multicenter clinical trial protocol designed to assess whether the administration of an additional pre-extubational loading dose of caffeine citrate improves extubation success in mechanically ventilated preterm

infants. Eligible infants are randomized to receive either standard maintenance caffeine therapy or an extra loading dose 1 hour before planned extubation. The primary outcome is extubation success at 48 hours. Adverse effects are also assessed. The trial protocol was developed in line with SPIRIT and CONSORT guidelines and registered prospectively.

4. Results

4.1. Study I- The histologic fetal inflammatory response and neonatal outcomes: systematic review and meta-analysis

The meta-analysis included 50 studies and examined a wide range of neonatal outcomes in relation to the presence of FIR. The pooled results demonstrated a statistically significant increase in the odds of early-onset sepsis, BPD, retinopathy of prematurity, and IVH among neonates with FIR. The presence of FIR was associated with three-fold elevated odds of clinical chorioamnionitis. No significant difference was found in case of mortality, late-onset sepsis, severe IVH, periventricular

leukomalacia, patent ductus arteriosus, respiratory distress syndrome, being small for gestational age, and cerebral palsy. FIR was associated with reduced odds of NEC in the subgroup with lower mean gestational age.

4.2. Study II- The route of intrauterine inflammation along the umbilical cord: a retrospective analysis of placental specimens from a 3-year cohort

Out of 237 evaluated cases, no IUI was detected in 154 cases. Among the 83 cases with IUI, MIR without FIR was observed in 34 cases. FIR was present only on the placental side in 23 cases, while in 24 cases, FIR was found at both the placental and fetal ends of the umbilical cord. The most advanced form, Stage 3 MIR, was significantly more frequent when inflammation extended to both ends of the cord. Furthermore, the presence of FIR was associated with a significantly higher incidence of IVH.

4.3. Study III - The effect of an additional pre-extubational loading dose of caffeine citrate on mechanically ventilated preterm infants (NEOKOFF

trial): Study protocol for a multicenter randomized clinical trial

The NEOKOFF trial protocol was designed to include 226 preterm infants <32 weeks' gestation requiring mechanical ventilation. The study's design is powered to detect a 16.8% absolute improvement in extubation success with 80% statistical power to identify a significant difference. The primary endpoint is successful extubation at 48 hours post-intervention. The trial aims to generate evidence for a simple, low-risk pharmacologic intervention that could enhance periextubation stability-

5. Conclusions

This thesis demonstrates that FIR is a meaningful clinical marker when evaluated not just by presence, but also by anatomical distribution. Integrating FIR into risk stratification may improve outcome prediction in preterm infants. Additionally, optimizing caffeine therapy during the periextubation period represents a feasible and promising intervention. These combined approaches offer a path toward more precise, evidence-driven neonatal care.

6. Bibliography

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