The Canadian Neonatal Network™/Le Réseau Néonatal Canadien™

2025 CNN-CPTBN Annual Meeting

Research Proposal

PROMETEO (Preterm Rupture Of MEmbranes-opTimal rEgimen for antibiOtic therapy): a pilot RCT

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Background and Importance

Preterm prelabor rupture of membrane (PPROM) is a major cause of preterm birth, often associated with bacterial invasion of the amniotic cavity. Antibiotic treatment following PPROM increases latency (time from membrane rupture to birth) and reduces complications for both pregnant persons and neonates. Current guidelines-recommended antibiotics regimens are based on trials from over 25 years ago, primarily targeting gram-positive organisms with ampicillin and erythromycin. However, neonatal early-onset sepsis pathogens have shifted from gram-positive group B Streptococcus to gram-negative Escherichia coli, and resistance to standard antibiotics has increased. This change highlights a critical gap in the current empiric antibiotic coverage for PPROM. There is an urgent need for studies evaluating the efficacy of third-generation cephalosporins, which offer better gram-negative coverage, to mitigate the adverse effects of PPROM on pregnant patients and their children. We hypothesize that an extended antibiotic regimen, with improved gram-negative coverage will reduce infectious morbidity and other severe neonatal outcomes.

Goal(s) / Research Aims

This pilot trial aims to assess the feasibility of a full-scale randomized control trial by exploring whether, in singleton pregnancies with PPROM at 23 0/7 to 33 6/7 weeks' gestation (P), randomization to an expanded antibiotic regimen (ceftriaxone/cefixime + azithromycin) (I) versus a standard regimen (ampicillin/amoxicillin + azithromycin) (C) enable recruitment of at least 40% of eligible individuals (O) within 12 months (T).

Methods / Approaches / Expertise

This open-label pilot trial will recruit PPROM cases within 24 hours from three tertiary centers in Quebec and Ontario. Exclusions include life-threatening fetal abnormalities, contraindications to expectant management (e.g., labour, chorioamnionitis, placental abruption, or non-reassuring fetal testing), recent antibiotic use (except antibiotics used within first 24 hours for PROM), allergy or contraindications to study antibiotics and prior trial participation. Recruitment will continue for 12 months or until 96 participants are enrolled, whichever comes first. Participants will be randomized 1:1 to receive extended or standard antibiotic treatment for seven days. Follow-up will extend to six weeks postpartum for participants and until hospital discharge for infants. Feasibility outcomes include the recruitment rate (percentage of enrolled/eligible candidates) as the primary outcome and protocol compliance, monthly recruitment rate, data entry and follow-up completeness, adverse reactions, and data collection time as secondary outcomes. Clinical outcomes will be collected but not compared until the full-scale trial. Success criteria include 1) recruiting at least 40% of eligible candidates; 2) approaching at least 70% of eligible candidates; 3) administering the study drug to 95% of participants within 24 hours of PPROM; 4) ensuring 95% of participants complete follow-up. The study will be conducted by a multidisciplinary team with expertise in maternal-fetal medicine, microbiology, neonatology, clinical epidemiology, clinical trials and patients' representatives from the Canadian Premature Babies Foundation.

Expected Outcomes

This pilot trial aims to provide critical data for preparation a full-scale multicentric pragmatic RCT to determine if an expanded antibiotic regimen for PPROM improves severe neonatal composite outcomes.