17-Hydroxyprogesterone Caproate to Prevent Preterm Birth in Triplet Pregnancy:
Protocol for an Individual Participant Data Meta-analysis

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Background

Triplet pregnancies are at very high risk for preterm birth and therefore at high risk for neonatal morbidity and mortality. In developed countries, 90-100% of triplets are delivered preterm (before 37 weeks of gestation) and 35-50% are delivered very preterm (before 32 weeks) [Battin, 2009; Geipel, 2003; Luke, 2007; Martin, 2013; Tandberg, 2010; Zuppa, 2007].

Major neonatal morbidity as reflected in admission to a neonatal intensive care unit complicates 50-90% of triplet births [Al-Suleiman, 2006; Battin, 2009; Chibber, 2013; Spencer, 2009], compared to about 3% of singletons and 24% of twins [Lemos, 2013]. Perinatal death occurs in 4.5-15% of triplets [Adegbite, 2005; Al-Suleiman, 2006; Bajoria, 2006; Battin, 2009; Chibber, 2013; Getahun, 2006; Spencer, 2009; Tandberg, 2010; Weissmann, 2013], compared to 0.45% of singletons and 2.0% of twins [Luke, 2007].

Most of the excess in neonatal morbidity and mortality among triplets is directly attributable to very preterm birth [Garite, 2005]. Thus, reduction in the rate of very preterm birth is a major goal of the management of triplet pregnancy.

Interventions to reduce preterm birth in triplets

Several interventions intended to reduce the rate of preterm birth have been tested in triplet pregnancy. Multifetal pregnancy reduction (MFPR) is perhaps the most promising. MFPR involves intentional feticide of one triplet, resulting in a twin pregnancy. There have been no randomized controlled trials (RCTs) of this procedure [Dodd & Crowther 2012]. A systematic review of retrospective studies comparing MFPR to conservative management in nearly 3,000 triplet pregnancies [Wimalasundera et al, 2003] found that MFPR was associated with substantial reductions very early preterm birth (10.1% vs 20.3%) and perinatal mortality (2.7% vs 9.2%). However, many women will not consider intentional feticide. MFPR requires terminating 33% of fetuses in order to reduce perinatal mortality by 6.5%.

Various other interventions have been tested, without success, in attempts to reduce the rate of preterm birth in triplet pregnancy, including:

- Prophylactic bed rest [Crowther and Han, 2010]
• Prophylactic cervical cerclage [Strauss et al, 2002; Rebarber et al, 2005]
• Prophylactic tocolytic medications. There have been no trials in triplets comparing prophylactic tocolysis to placebo or no treatment. A small uncontrolled series of triplet pregnancies treated with terbutaline pump therapy reported a mean gestational age of 33 wks at delivery [Elliott, 1997], similar to that seen in untreated triplet pregnancy [Crowther and Han, 2010; Rebarber et al [2005].

Given the failure of these methods, other interventions to reduce the rate of preterm birth in triplet pregnancy are desired. One approach that has received extensive attention in the past decade is the prophylactic use of progestogens.

Progestogens to prevent preterm birth

RCTs in singleton pregnancies have suggested that antenatal progestogen treatment using vaginal progesterone or 17-hydroxyprogesterone caproate (17OHPc) prevents preterm delivery in women who are at high risk of preterm birth because of a history of a prior preterm birth [da Fonseca, 2003; Meis, 2003] or a short cervix [Romero, 2012]. These trials have led investigators to examine whether antenatal progestogens could decrease preterm birth in multiple pregnancies. In twin pregnancy, neither vaginal progesterone nor 17-OHPc appears effective at reducing preterm birth, perinatal morbidity, or perinatal mortality [Schuit, 2014].

Two RCTs of 17OHPc to prevent preterm birth in triplet pregnancy have been published [Caritis, 2009; Combs, 2010]. Two other trials had an inclusion criterion of “multiple gestation” and included mostly twins but also a few triplets [Lim, 2011; Wood 2012]. Key elements of these trials are summarized in Table 1. None of the trials showed a significant effect of progestogen on the rate of preterm birth.

Rationale for an individual participant data meta-analysis

Meta-analysis involves synthesis of estimates from multiple clinical trials. This allows more robust estimates of overall treatment effects as well as evaluation of potential harms. The latter is particularly important because one trial found that 17OHPc was associated with increased risk of midtrimester pregnancy loss in triplet pregnancy [Combs, 2010], though this was not noted in the other studies.
Table 1. Published studies of progestogens to prevent preterm birth in triplets

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caritis, 2009</td>
<td>134</td>
<td>17-OHPc</td>
<td>Placebo</td>
<td>Delivery or fetal loss before 35 weeks</td>
</tr>
<tr>
<td>Combs, 2010</td>
<td>75</td>
<td>17-OHPc</td>
<td>Placebo</td>
<td>Composite adverse neonatal outcome</td>
</tr>
<tr>
<td>Lim, 2011</td>
<td>17</td>
<td>17-OHPc</td>
<td>Placebo</td>
<td>Composite adverse neonatal outcome</td>
</tr>
<tr>
<td>Wood, 2012</td>
<td>3</td>
<td>Micr Prog</td>
<td>Placebo</td>
<td>Gestational age at delivery</td>
</tr>
</tbody>
</table>

N = total number of mothers with triplet pregnancy  
17-OHPc = 17-hydroxyprogesterone caproate, intramuscular, 250 mg weekly  
Micr Prog = micronized progesterone in bioadhesive gel, vaginally, 90 mg daily

Traditional meta-analysis uses aggregated data, typically using the published summary numbers or group totals from each trial. A problem with aggregated data meta-analyses (ADMA) is that independent trials often have different primary outcomes and different defined subgroups, making it impossible to pool the results.

Individual participant data meta-analysis (IPDMA) overcomes this problem as it involves synthesis of individual level data from clinical trials. This allows for the same robust estimate of the treatment effect and harmful effects as in ADMA and further allows more flexibility regarding the choice of endpoints, subgroups and potential harms.

IPDMA has several distinct advantages over ADMA:

- IPDMA allows standardization of inclusion and exclusion criteria and analysis across studies, independent of bias that may arise through selective reporting [Riley, 2010].
- IPDMA allows for exploration of a differential treatment effect in relevant subgroups (i.e. treatment covariate interactions), for example, women with a short cervix [Simmonds, 2005]. Since IPDMA includes more detailed data than ADMA, statistical power to carry out informative subgroup analyses is higher. Furthermore, flexibility of subgroup analyses is enhanced, thus the estimated subgroup effects may be less influenced by misclassification and bias. IPDMA therefore allows for a valid assessment of differences in treatment effects across
subgroups [Thompson & Higgins, 2005].

- IPDMA allows time-to-event analysis whereas ADMA only allows a pooled estimate of treatment effect at specified cut-points, e.g. delivery before 32, 34 or 37 weeks. The combined analysis of individual data however, can take account of the time between the initiation of treatment and the outcome of interest [Clarke, 2005]. Time-to-delivery analysis (e.g., Kaplan-Meier survival plots, Cox regression) enables exploration of associations between the timing and duration of progestogen treatment and outcomes such as preterm birth or intrauterine death. This may be important because small differences in duration of pregnancy attributable to progestogens may have been missed in the individual trials owing to small sample size.

**Proposed Methods**

**Criteria for inclusion of studies in IPDMA**

We propose an IPDMA of RCTs comparing 17OHPc to placebo in women with triplet pregnancy. We will also consider inclusion of quasi-randomized studies or studies comparing progestogen to either “no treatment” or “standard care” rather than placebo (i.e. “open-label” studies rather than “blinded” or “masked” studies), though we are not currently aware of any such trials.

Our interest includes progestogens other than 17OHPc, specifically vaginal progesterone. To our knowledge, however, only 3 subjects with triplet pregnancy have been included in an RCT of vaginal progesterone [Wood, 2012]. Because this agent is substantially different than 17OHPc [Romero, 2013], we do not believe that it makes sense to attempt to include these 3 subjects in an IPDMA that is overwhelming dominated by trials of 17OHPc. Unless an updated literature search identifies other trials involving vaginal progesterone, we plan to reference the Wood trial, but not include those subjects in the IPDMA.

**Participants**

Inclusion criteria will be women with triplet pregnancy who were included in a clinical trial of 17OHPc versus control for the prevention of preterm birth. We will tabulate the
details of inclusion and exclusion criteria used in the individual trials, comparing and contrasting similarities and differences.

Identification of studies

In February, 2014, we performed an electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE and ClinicalTrials.gov for published or registered randomized controlled trials including women with triplet pregnancy randomly allocated to treatment with progestogens (including micronized progesterone and 17-OHPc) versus control (placebo or no treatment) in the second or third trimester with the intention to prevent preterm birth. We tested various combinations of the search terms progesterone, hydroxyprogesterone, caproate, progestogen, progestin, preterm birth, perinatal morbidity, perinatal outcome, triplets, and pregnancy, multiple. We reviewed the title and abstract information from retrieved citations and obtained full text citations as needed to determine relevance. We also reviewed lists of citations in related articles and review articles. The 4 studies listed in Table 1 were the only ones judged to meet the basic inclusion criteria: triplet pregnancy and RCT comparing progestogen to control.

The principal investigators (PI) from the three studies of 17OHPc agreed to collaborate in this IPDMA. One of the authors (ES) already has the de-identified data in-hand from the 4 known trials that included triplets (Caritis, 2009; Combs, 2010; Lim, 2011; Wood, 2012). However, as of June, 2014, we are awaiting permission from the trial coordinating committee of one of the trials to use their data for the proposed meta-analysis.

We will update the electronic search for trials after we have permission to use the data from that trial and after registering the metanalysis protocol with PROSPERO, an international prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO/).

Risks of bias will be assessed in all of the identified studies using a tool developed by the Cochrane collaboration [Higgins & Green, 2011], including the following criteria:

- sequence generation (i.e. computer generated random number, use of random number table or other truly random process)
- allocation concealment (i.e. web-based or telephone central randomization or
consecutively numbered sealed opaque envelopes)

• blinding for participants, study personnel and outcome assessors
• Incomplete outcome data
• Selective outcome reporting
• Other sources of bias

According to the Cochrane Handbook, each item of bias will be scored as low, high or unclear. All the items will be scored 4 times, once by the PI of each included study (SC, AC, or AL) based on first-hand knowledge of the trial, once by each of the other two PIs based on the published papers, and once by the epidemiologist (ES) based on the published papers. If 3 or 4 of these assessments are in agreement, the majority will rule. In the event of a tie, a fifth investigator (BJWM) will also score risks of bias to break the tie.

We will exclude studies for any of these reasons:

• investigator(s) decline to provide data for IPDMA
• more than 10% attrition or exclusion of patients after randomization
• incomplete reporting of reasons for withdrawals and protocol violations
• imbalance in drop-outs across groups
• incomplete reporting of all the study’s pre-specified outcomes
• outcomes of interest made not made available for analysis

Outcome measures

The primary outcome will be adverse perinatal outcome, defined as any one or more of the following:

• miscarriage (fetal death and/or spontaneous expulsion <20 wks gestational age
• stillbirth (fetal death at ≥20 wks gestational age)
• neonatal death (death of liveborn infant at less than 28 days of life (Barfield, 2011))
• respiratory distress syndrome (RDS) requiring ventilation for ≥ 24 hr
• bronchopulmonary dysplasia (BPD)
• intraventricular hemorrhage (IVH) grade III or IV
• periventricular leucomalacia (PVL)
• necrotizing enterocolitis (NEC) grade II or more
• culture proven sepsis,
• retinopathy of prematurity (ROP) requiring treatment

Secondary outcomes will be
• Each of the individual component outcomes of the primary outcome
• Birth < 28 wks
• Birth < 32 wks
• Birth < 34 wks
• Pregnancy loss < 24 wks (birth, stillbirth, or miscarriage)
• Pregnancy loss < 28 wks
• Pregnancy loss < 32 wks
• Pregnancy loss < 34 wks
• Time from randomization to outcome (birth or fetal death)

Subgroup analyses
Subgroup analyses will be performed for the primary outcome in the following subgroups:

• women with a cervical length <30th percentile on baseline assessment (in studies where transvaginal cervical length measurement was specified in the protocol)
• women with a prior spontaneous preterm birth < 37 weeks

Analysis
Overall effects of 17OHPc treatment in women with triplet pregnancies will be estimated in the pooled IPD. Descriptive comparisons between studies will be conducted to assess between-study differences. If necessary, we assume the data to be missing at random (MAR), therefore observed patient characteristics will be used to impute missing data, by means of multiple imputation [Donders, 2006]. Missing data will be imputed within each original study, before data of the individual studies are pooled to preserve between-study heterogeneity. Treatment effects on the mother level will be estimated by means of a random intercept (to account for baseline differences among studies) fixed effects (effect of 17OHPc is assumed to be equal among studies) log-binomial model and, hence, the measure of association is the risk ratio. The effectiveness of treatment for
outcomes on the child level were estimated using a binomial generalised estimating equations with a log-link function to account for clustering of children within one mother [Gates, 2004]. The presence of heterogeneity of outcomes across trials will be assessed using the I² measure with values interpreted as follows: 0% indicates no observed heterogeneity; 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively [Higgins, 2003]. When heterogeneity is found to be high a random effect will be fitted for each study as well, otherwise a fixed effect will be used. When for an outcome the heterogeneity is 50% or higher we will use a random effects model to investigate whether this approach better fits the data. Akaike’s Information Criterion (AIC) of the random effects model will be compared to the fixed effects model and the model with the lowest AIC will be used as the final model for analysis. If necessary, analyses will be adjusted for variables used in stratified randomization. Number-needed–to-treat or number-needed-to-harm with 95% confidence is planned if a treatment effect is found to be statistically significant.

Since the effectiveness of treatment is mainly judged on effects on early preterm birth and not necessarily on overall gestational age at delivery we will apply a two-part model to estimate the effect of 17OHPc on the combined endpoint of preterm birth (i.e., birth before 34, 32, and 28 weeks), and gestational age at delivery for those who are born preterm. A two-part model combines the probability of preterm birth estimated using a log-binomial regression model with the median gestational at delivery in those with a preterm birth estimated using linear quantile regression. Confidence intervals will be constructed with bootstrapping (1000 samples).

Subgroup effects will be investigated using an interaction term between the subgroup and the treatment in the regression model. If an interaction is found to be significant (p < 0.05), a stratified analysis will be performed to investigate the effect of progestogen treatment in different strata of the subgroups.

Time-to-delivery analysis will be performed with Kaplan-Meier analysis and Cox proportional hazards regression analysis. Again, dependency between data originating from the same study will be taken into account by conducting a stratified analysis.

**Discussion**

We believe that the proposed IPDMA will help to determine whether 17OHPc treatment in triplet pregnancy is beneficial or harmful. This is the first study that combines data on the effect of progestogens in triplet pregnancies and the proposed IPDMA methodology will maximize the impact of results.

The protocol for the IPDMA has been designed with input from the principal investigators of 3 RCTs of 17OHPc in women with triplet pregnancies (Table 1). All authors have committed to providing data if their studies meet inclusion criteria. In total these trials have included 226 women and their 678 offspring, allowing the meta-analysis to explore effects of progestogens on uncommon outcomes and possibly in high-risk subgroups. We anticipate it will provide a definitive data synthesis guiding clinical practice and future research in this area.

**References**


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FIGO Committee for the Ethical Aspects of Human Reproduction and Women’s Health.


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