Timing of delivery for women with non-severe hypertensive disorders of pregnancy
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Relevance of individual participant data meta-analysis for studies in obstetrics: delivery versus expectant monitoring for hypertensive disorders of pregnancy


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Abstract

Like many other research subjects in obstetrics, research on immediate delivery versus expectant monitoring for women with hypertensive disorders of pregnancy faces certain challenges when it comes to interpretation and generalisation of the results; relatively rare outcomes are studied, in a clinically heterogeneous population, while the clinical practice in some countries has dictated that studies in term pregnancy were completed before earlier gestational ages could be studied. This has resulted in multiple smaller studies, some studying surrogate outcome measures, with different in- and exclusion criteria, and without enough power for reliable subgroup analyses. All this complicates the generation of definitive answers and implementation of the results into clinical practice. Performing multiple studies and subsequently pooling their results in a meta-analysis can be a way to overcome the difficulties of studying relatively rare outcomes and subgroups with enough power, as well as a solution to reach a final answer on questions involving an uncertain and possibly harmful intervention. However, in the case of the current studies on delivery versus expectant monitoring in women with hypertensive disorders of pregnancy, differences regarding eligibility criteria, outcome measures and subgroup definitions make it difficult to pool their results in an aggregate meta-analysis. Individual patient data meta-analysis (IPDMA) has the potential to overcome these challenges, because it allows for flexibility regarding the choice of endpoints and standardization of inclusion and exclusion criteria across studies. In addition, it has more statistical power for informative subgroup analyses. We therefore propose an IPDMA on immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy, and advocate the use of IPDMA for research questions in obstetrics that face similar challenges.
Research in obstetrics frequently faces challenges when it comes to interpretation and generalisation of the results, thus hampering implementation of results into clinical practice. We advocate the use of Individual Patient Data Meta-Analysis (IPDMA) as a method to overcome these challenges, using research on delivery versus expectant monitoring for hypertensive disorders of pregnancy as an example.

Approximately 10% of all pregnancies are complicated by hypertensive disorders of pregnancy (HDP), including gestational hypertension (GH), preeclampsia (PE), chronic hypertension (CH) and preeclampsia superimposed on chronic hypertension (sPE). Hypertensive disorders of pregnancy remain one of the main causes of maternal and perinatal morbidity and mortality worldwide.

Thus far, delivery of the child and subsequent delivery of the placenta is the only definitive treatment for HDP. However, delivery itself can also negatively affect pregnancy outcomes; immediate delivery can implicate preterm birth, which is associated with an increased risk of neonatal morbidity and mortality. In addition, it was historically believed that induction of labour was associated with an increased risk of caesarean section, though recent meta-analyses of randomised clinical trials have indicated otherwise.

In recent years, several studies comparing immediate delivery and expectant monitoring in women with HDP ≥34 weeks of gestation have been conducted or planned. However, single studies have limitations that complicate the interpretation and generalisation of their results, as we will illustrate by the discussion following publication of the HYPITAT trial.

In the HYPITAT trial, 756 women with mild GH or PE and a gestational age ≥36 weeks were randomly allocated to either induction of labour or expectant monitoring. The primary outcome measure was a composite of poor maternal outcomes consisting of maternal mortality, eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, placental abruption, major postpartum haemorrhage or progression to severe hypertensive disease (systolic blood pressure ≥170 mm Hg, diastolic blood pressure ≥110 mm Hg, or proteinuria ≥5 g per 24 h)). This outcome was significantly less frequent in women who were...
randomised for induction of labour as compared to women who were monitored expectantly (31% vs. 44%, RR 0.71, 95% confidence interval (CI) 0.59–0.86).

The interpretation of the HYPITAT results was subject of debate. Firstly, the use of severe hypertension as a component of the primary outcome was not unanimously accepted, as some critics argued that severe hypertension without other complications is not an adverse outcome justifying early delivery. Secondly, heterogeneity of the included women, both with respect to gestational age and with respect to the type of hypertensive disorder led to different interpretations.

In the Netherlands, where the HYPITAT trial was conducted, the study resulted in an increase in induction of labour among all women with HDP at term, both women with GH and women with PE. Conversely, the UK National Institute for Health and Clinical Excellence guideline on hypertension in pregnancy advises induction of labour only for women with PE at term, arguing that analysis stratified for type of HDP did not demonstrate a significant reduction of progression to severe disease in women with GH in the HYPITAT trial.

The debate following publication of this trial clearly illustrates the limitations of any single study that investigates the impact of delivery versus expectant monitoring for women with HDP ≥34 weeks of gestation. Serious adverse outcomes with a high probability of mortality or long-term morbidity are rare in these women and their neonates. Therefore, studying genuine adverse outcomes, as opposed to surrogate outcomes (such as severe preeclampsia or progression to severe disease), requires a very large sample size. However, in the reality of clinical research, trials of this size are usually not feasible in terms of funding, organisation and study duration, even if they are performed at multiple sites. Consequently, a trial on hypertensive disorders of pregnancy will usually require a compromise between studying relevant outcomes with sufficient power on one hand and feasibility on the other hand, and will therefore not provide a definitive answer by itself.

This issue becomes even more pronounced if the clinical heterogeneity of hypertensive disorders is taken into account. This heterogeneity has inspired countless attempts to identify subgroups of women who are at higher risk of adverse outcomes than others. However, trials allowing for reliable subgroup analyses require a larger sample size, whereas trials including only one subgroup take longer to complete, which further complicates the discussion on power versus feasibility.
Another argument to conduct separate trials for several subgroups is uncertainty about the effectiveness and possible harms of the intervention. Prior to the HYPITAT study, there was debate on the effectiveness of delivery in women with hypertensive disorders in the Netherlands. There were concerns about the harmful effects of induction of labour on the course of delivery and about neonatal outcomes at earlier gestational ages. As a consequence, at that time it was neither practically feasible nor ethically justified to include all women with hypertensive disorders regardless of gestational age in one big trial immediately. Only after HYPITAT had shown that delivery was not harmful and potentially beneficial for women with hypertensive disorders at term and their children, could the subsequent HYPITAT-II study assess delivery in women with a gestational age between 34 and 37 weeks. As such, a strategy of one study following the other, titrating towards the overall answer, can be more effective than one large study solving the whole problem at once. Whether this applies is largely dependent on the local or national situation. For example, while the clinical setting in the Netherlands justified HYPITAT, clinical practice in the United States at that time allowed for a study that randomised women with preeclampsia at a gestational age between 34 and 37 weeks.\textsuperscript{15}

Performing multiple studies and subsequently pooling their results in a meta-analysis can be a way to overcome the difficulties of studying relatively rare outcomes and subgroups with enough power, as well as a solution to reach a final answer on questions involving an uncertain and possibly harmful intervention. However, in the case of the current studies on delivery versus expectant monitoring in women with hypertensive disorders of pregnancy, differences regarding eligibility criteria, outcome measures and subgroup definitions make it difficult to pool their results in an aggregate meta-analysis. Individual Participant Data (IPD) meta-analysis has the potential to overcome this problem. IPD meta-analysis (IPDMA) involves collecting and reanalysing original datasets. This allows for flexibility regarding the choice of endpoints as well as the classification of subgroups. In addition, IPD include more detailed data on a participant level than aggregated data meta-analyses, so the statistical power for informative subgroup analyses is higher. Finally, IPD allows standardization of inclusion and exclusion criteria across studies, independently of bias that may arise through selective reporting.\textsuperscript{16-18}

We have therefore established a collaboration with the aim of performing an IPDMA of randomised controlled trials comparing delivery with expectant monitoring.
for women with hypertensive disorders of pregnancy ≥34 weeks of gestation. We performed an electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE and ClinicalTrials.gov for published or registered randomised controlled trials including women with a pregnancy related hypertensive disorder that were randomly allocated to planned delivery or expectant monitoring. Cluster-randomised trials or studies with a quasi-random design were excluded. We used the search terms (“hypertensive disorders of pregnancy” OR “pregnancy induced hypertension” OR “gestational hypertension” OR (“pre-eclampsia” OR “preeclampsia”) OR ((“hypertension” AND (“chronic” OR “chronical*” OR “pre-existent” OR “preexistent”)) AND “Pregnancy”)), with the limits “human” and “randomised controlled trial”. Authors of included trials were asked whether they were aware of other relevant studies that we had not identified so far. Readers of this publication are also invited to approach us with such information.

The corresponding authors of the eligible studies that have been identified up to now have been approached to participate, to comment on the draft protocol, and to provide raw data or use the data sheet that was drafted in conjunction with the protocol. At present, our collaboration includes the HYPITAT, HYPITAT-II and DIGITAT trials,\textsuperscript{10,19,20} the “Deliver or Deliberate” trial,\textsuperscript{15} and the ongoing PHOENIX trial (http://www.controlled-trials.com/ISRCTN01879376).

The first outcome measure that we will study is a composite measure of maternal mortality and severe maternal morbidity (eclampsia, stroke, cardiac arrest, pulmonary edema, renal failure, liver failure, HELLP syndrome, disseminated intravascular coagulation, placental abruption/antenatal haemorrhage, and/or thromboembolic disease). In addition, we will study a composite measure of perinatal death and significant neonatal morbidity (respiratory distress syndrome, bronchopulmonary dysplasia, seizures, intracerebral haemorrhage, intraventricular haemorrhage grade III or IV, cerebral infarction, periventricular leucomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis grade II or more, or culture proven sepsis). Detailed definitions and secondary outcome measures are described in the protocol available in appendix A.

Analyses will include descriptive comparisons between studies to assess between-study differences and the amount of missing data. In cases we judge absent data to be missing at random, observed participant characteristics will be used to
impute missing values by means of multiple imputation. Treatment effects will be estimated in each of the resultant IPD sets and pooled using Rubin's rules. Summary measures of the treatment effects will be estimated using a random effects log-binomial multi-level regression model. The presence of heterogeneity of outcomes across trials will be assessed using the I2 measure. A random intercept will be fitted for each original study to account for heterogeneity across studies and dependency between observations originating from the same study. To investigate subgroup effects (also detailed in the protocol provided appendix A), we will estimate treatment-covariate interactions using all available data in a single model. When the within-trial interaction is significant (p<0.1), the treatment effect will be estimated within strata based on the subgrouping variable.

In our opinion, the proposed methodology will maximise the use of data that is already available. In addition, the IPDMA has the potential to guide future research in this area. In addition to updating the analysis at regular intervals by adding results of published studies, we hope to be able to use it to identify knowledge gaps and to generate new hypotheses, so we can prospectively direct future research efforts.

As many research questions in obstetrics face the similar challenges, IPDMA is a promising method to facilitate interpretation and implementation of results on other subjects too. Prospective collaboration and design, such as for example in the international STRIDER IPD study group, would be ideal, as it allows for advance agreement on a common core data set. In situations where such a scenario is not possible, consensus on core outcomes for trials in obstetrics, such as those that are currently being developed within the CROWN initiative, would greatly facilitate retrospective IPDMA.

In summary, like many other research subjects in obstetrics, single studies on the subject of delivery versus expectant monitoring for women with hypertensive disorders of pregnancy at or beyond 34 weeks of gestation face limitations as a result of serious adverse outcomes being rare and the clinical heterogeneity of the study population. These limitations cannot be overcome by traditional meta-analysis, since available studies have used different definitions for eligibility criteria, outcome measures, and subgroup variables. Individual participant data meta-analysis has the potential to overcome these problems and to provide more definitive evidence to guide clinical practice and to guide future research.
Chapter 8

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Appendix A Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy at or near term: a protocol for an individual participant data meta-analysis of randomised controlled trials


Abstract

Background Approximately 5-10% of pregnancies are complicated by hypertensive disorders of pregnancy. These disorders contribute significantly to maternal morbidity and perinatal morbidity worldwide. Since delivery is the only definitive treatment for these disorders, planned delivery by induction of labour or elective caesarean section prevents maternal complications compared to expectant management. On the other hand, planned delivery might increase the risk of neonatal mortality and morbidity due to preterm delivery or increase complications resulting from instrumental delivery and caesarean section.

Design We plan an individual participant data meta-analysis of randomised, controlled trials of planned delivery versus expectant monitoring, in women with hypertensive disorders of pregnancy at or near term. The primary outcomes will be adverse maternal and perinatal outcomes. Missing data will preferentially be managed by multiple imputation and variables will be recoded within each original study, before pooling the studies. The summary effects of induction of labour will be estimated by means of random effects log-binomial models. Analyses will be adjusted for variables used in stratified randomization when indicated. Pre-specified subgroup analyses will be performed.

Discussion Combining individual participant data from different randomised trials has potential to provide valuable, clinically useful information regarding the benefits and potential harms of planned delivery for women with hypertensive disorders of pregnancy overall and in relevant subgroups.
Background

HYPERTENSIVE DISORDERS OF PREGNANCY
Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, chronic hypertension and preeclampsia superimposed on chronic hypertension. Approximately 5-10% of pregnancies are complicated by hypertensive disorders, with rates being reported to increase over the last decennia. Hypertensive disorders of pregnancy can occur near term presenting with mild hypertension and without apparent fetal compromise. In other cases, the onset is preterm, with increased risk of complications such as eclampsia, placental abruption, HELLP syndrome, fetal growth restriction, or fetal death. The clinical heterogeneity of these disorders might reflect differences in underlying pathophysiology.

PLANNED DELIVERY VERSUS EXPECTANT MONITORING
Delivery of the placenta is the only definitive treatment for hypertensive disorders of pregnancy. Prolongation of a pregnancy complicated by a hypertensive disorder by stabilisation and close monitoring of the mother and her fetus (expectant monitoring) increases the risk of progression of the disease and the development of complications. Planned delivery by induction of labour or elective caesarean section could prevent those complications, but may increase the risk of instrumental delivery and caesarean section, thereby leading to increased risk of maternal morbidity. Moreover, planned delivery can result in preterm delivery and related neonatal morbidity and mortality.

Published randomised controlled trials comparing planned delivery with expectant monitoring for hypertensive disorders at or near term are scant. They cover various types of hypertensive disorders at various gestational ages, use different definitions for inclusion as well as outcome criteria, have different baseline characteristics, and use different intervention protocols. Therefore, general conclusions are difficult to draw. Combining individual participant data from clinical trials has the potential to overcome these difficulties and to provide valuable information regarding the optimal timing of delivery for women with a hypertensive disorder at or near term.

RATIONALE FOR AN IPD META-ANALYSIS
Aggregated data meta-analysis involves synthesis of group-based estimates from clinical trials. This allows for an estimate of the overall treatment effect as well as
any harmful effects. A potential problem in aggregated data meta-analyses is that primary outcomes of clinical trials as well as subgroups defined in clinical trials can differ, which makes it impossible to obtain summary estimates. An Individual Participant Data (IPD) meta-analysis can overcome this problem as it involves synthesis of individual level data from clinical trials. This can lead to a more robust estimate of the treatment effect and of harmful effects, allowing for more flexibility regarding the choice of endpoints and subgroups.

Performing an IPD meta-analysis compared to aggregated data meta-analysis has further advantages. Firstly, IPD allows standardization of inclusion and exclusion criteria and analysis across studies, independent of bias that may arise through selective reporting. Secondly, IPD allows for exploration of a differential treatment effect in relevant subgroups (i.e. treatment-covariate interactions), for example, (age, ethnicity, gestational age, type of disease) without the risk of ecological bias. Since IPD meta-analyses include more detailed data on a participant level than aggregated data meta-analyses, the 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. IPD meta-analysis therefore allows for a valid assessment of differences in treatment effects across subgroups.

We propose an IPD meta-analysis of randomised controlled trials of planned delivery versus expectant monitoring for women with hypertensive disorders of pregnancy at or near term.

Methods

CRITERIA FOR INCLUSION OF STUDIES
We will include randomised controlled trials comparing planned delivery with expectant monitoring of women with hypertensive disorders of pregnancy at or near term.

IDENTIFICATION OF TRIALS
We will perform an electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE and ClinicalTrials.gov for published
or registered randomised controlled trials including women with a pregnancy related hypertensive disorder that were randomly allocated to planned delivery or expectant monitoring. Cluster-randomised trials or studies with a quasi-random design will be excluded. We will use the search terms ("hypertensive disorders of pregnancy" OR "pregnancy induced hypertension" OR "gestational hypertension" OR ("pre-eclampsia" OR "preeclampsia") OR ("hypertension" AND ("chronic" OR "chronical*" OR "pre-existent" OR "preexistent")) AND "Pregnancy")), with the limits “human” and “randomised controlled trial”. Authors of included trials will be asked whether they are aware of studies that we have not identified so far and readers of this protocol are also invited to approach us with such information.

Two review authors (KB and NN) will independently assess inclusion criteria, study quality and risk of bias. Disagreement will be resolved by discussion or, if necessary, by consultation of a third author (BWJM). When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Risks of bias will be assessed and classified into low, high, or unclear risk of in all of the identified studies based on the Cochrane Collaboration’s tool for assessing risk of bias in randomised trials:\textsuperscript{11}

- sequence generation (i.e. computer generated random number, use of random number table or other truly random processes)
- allocation concealment (i.e. web-based or telephone central randomisation or consecutively numbered sealed opaque envelopes)
- blinding for outcome assessors (blinding of participants or study personnel is not possible for the intervention)
- incomplete outcome data
- selective outcome reporting
- other sources of bias.

The corresponding authors of eligible studies will be approached to take part in the IPD meta-analysis. They will be asked to provide their data using the data sheet that was drafted in conjunction with this protocol, or to provide raw data. Data will then be interpreted and reformatted in consultation with the authors.

At present, our collaboration includes representatives of the HYPITAT-I,\textsuperscript{12} HYPITAT-II,\textsuperscript{13} DIGITAT,\textsuperscript{14} and “Deliver or Deliberate” trials,\textsuperscript{15} as well as a
IPDMA in obstetrics

representative of the ongoing PHOENIX trial (http://www.controlled-trials.com/ISRCTN01879376).

PARTICIPANTS
From the included trials, data from women aged ≥ 18 years, with gestational hypertension, preeclampsia, chronic hypertension or preeclampsia superimposed on chronic hypertension, and a gestational age ≥34 weeks will be collected. Gestational hypertension will be defined as a diastolic blood pressure ≥ 90 mmHg, measured at least twice 4 hours to 7 days apart, arising after 20 completed gestational weeks, in formerly normotensive women. Preeclampsia will be defined as gestational hypertension combined with proteinuria ≥ 0.3 g/24 hours or urine protein to creatinine ratio (PCR) ≥ 30 mg/mmol arising after 20 completed gestational weeks in formerly non-proteinuric women. Chronic hypertension will be defined as a diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medication before 20 completed weeks of gestation. Superimposed preeclampsia will be defined as chronic hypertension combined with proteinuria ≥ 0.3 g/24 hours or PCR ≥ 30 mg/mmol arising after 20 completed gestational weeks in formerly non-proteinuric women.1 Women with a multiple pregnancy will be included, as well as women with a fetus in non-cephalic presentation.

We will not include data from women with relevant co-morbidity and women with severe disease at inclusion (diastolic blood pressure ≥ 110 mmHg despite medication, systolic blood pressure ≥ 170 mmHg despite medication, HELLP syndrome, proteinuria ≥ 5g/24h, oliguria < 500 mL/24h, pulmonary edema or cyanosis, severe preeclamptic complaints). Cases with a non-reassuring fetal heart rate, abnormal umbilical artery pulsatility index or (suspected) congenital abnormalities including abnormal karyotype will not be included either, nor will women with ruptured membranes.

We will exclude subgroups from the analysis if there is reason to suspect a relevant difference in treatment effect in that subgroup, but little possibility of conducting a meaningful subgroup analysis. Based on the trials known to us so far, this means we will exclude women with a history of more than 1 caesarean section, a multiple pregnancy, and/or pre-existent or gestational diabetes. These criteria will be re-evaluated for future updates of this study.
Chapter 8

INTERVENTION
The intervention consists of planned delivery, either by induction of labour (preceded by cervical ripening following local protocol when indicated) or by elective caesarean section when vaginal delivery is contra-indicated. Expectant monitoring consists of stabilisation of the mother including the start of antihypertensive medication when indicated, followed by in- or outpatient observation until either spontaneous delivery occurs or an indication for delivery arises.

OUTCOME MEASURES
The first primary outcome measure will be adverse maternal outcome, a composite outcome of maternal mortality and severe maternal morbidity. Maternal mortality will be defined as death of a woman during pregnancy or before 42 days post-partum. Severe maternal morbidity will be defined as one or more of eclampsia, stroke, cardiac arrest, pulmonary edema, renal failure, liver failure, HELLP syndrome, disseminated intravascular coagulation, placental abruption/antenatal haemorrhage, and/or thromboembolic disease. Eclampsia will be defined as severe gestational hypertension or preeclampsia resulting in maternal seizures. Renal failure will be defined as a threefold increase in the serum creatinine, a 75% GFR decrease, urine output of less than 0.5 ml/kg per hour for 24 hours, or anuria for 12 hours. Liver failure will be defined as the rapid impairment of synthetic function and development of encephalopathy. HELLP syndrome will be defined as a complication of severe preeclampsia involving haemolysis, elevated liver functions, and low platelets. Thromboembolic disease will be defined as deep-vein thrombosis confirmed by duplex doppler, and/or pulmonary embolism confirmed by pulmonary angiography, computed tomography, magnetic resonance imaging or a ventilation-perfusion lung scan.

The second primary outcome will be adverse perinatal outcome, a composite outcome of perinatal death and significant neonatal morbidity. Perinatal death will be defined as stillbirth or neonatal death before 28 days post-partum or final discharge, whichever comes last. Significant neonatal morbidity will be defined as one or more of respiratory distress syndrome (RDS) requiring ventilation for ≥24hr, bronchopulmonary dysplasia (BPD), seizures, intracerebral haemorrhage, intraventricular haemorrhage (IVH) grade III or IV, cerebral infarction,
periventricular leucomalacia (PVL), hypoxic ischemic encephalopathy (HIE), necrotizing enterocolitis (NEC) grade II or more, or culture proven sepsis.

Secondary maternal outcomes will be severe hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure > 110 mmHg), severe proteinuria (> 5 g/24h), post-partum haemorrhage (>500 ml), caesarean section rate, instrumental vaginal delivery rate, morbidity related to caesarean section (wound infection, wound dehiscence, endometritis, postpartum haemorrhage (> 500 ml), urinary or bowel problems, venous thrombosis), and morbidity related to induction of labour (uterine hyperstimulation, uterine rupture, hyponatraemia, hypotension, chorioamnionitis, cord prolapse, failed induction (caesarean section for failure to progress in first stage).

Secondary neonatal outcomes will be Apgar score < 7 at 5 minutes, umbilical artery pH ≤ 7.0, hypoglycaemia, hyperbilirubinaemia, meconium aspiration syndrome, pneumothorax or pneumomediastinum, and mechanical ventilation. In addition we will investigate rates of intensive care admission for women and neonates.

ANALYSIS
First, descriptive comparisons between studies will be conducted to assess between-study differences and the amount of missing data. In cases we judge absent data to be missing at random (MAR) observed participant characteristics will be used to impute missing values by means of multiple imputation. These imputation sets will be combined into IPD sets by combining the first imputation sets for every study into the first IPD set, the second imputations sets into the second IPD set and so on. Treatment effects will be estimated in each of the IPD sets and pooled using Rubin’s rules.  

Second, summary measures of the treatment effects will be estimated using a random effects log-binomial regression model; the corresponding measure of association is the risk ratio. The presence of heterogeneity of outcomes across trials will be assessed using the I² measure. A random intercept will be fitted for each original study to account for heterogeneity across studies and dependency between data originating from the same study. When stratified randomization applied, analyses will be adjusted for variables used for stratification.
Chapter 8

**SUBGROUP ANALYSES**

To investigate subgroup effects on primary outcomes, we will estimate treatment-covariate interactions using all available data in a single model. The interaction terms in the model will be two independent terms representing across- and within-trial interaction effects. When the within-trial interaction is significant (p<0.1), the treatment effect will be estimated within strata based on the subgrouping variable. We aim to investigate treatment interactions with the following factors:

- gestational age
- type of hypertensive disorder
- presence or absence of suspected fetal growth restriction (estimated fetal weight <p10)
- systolic and diastolic blood pressure at randomization.
- parity
- ethnicity
- maternal age
- cervical length at randomization
- Bishop score at randomization
- BMI at booking.

For future updates of the analysis, we will also consider analysing treatment interactions with:

- multiple pregnancy
- pre-existent and/or gestational diabetes
- presence of a contra-indication for vaginal delivery
- history of ≥1 caesarean section.

**Discussion**

We propose an IPD meta-analysis on delivery versus expectant monitoring in women with hypertensive disorders of pregnancy ≥34 weeks of gestation. The proposed methodology will maximise the use of data that is already available and has several advantages over traditional aggregated data meta-analysis: the same inclusion and exclusion criteria can be applied to all participants, the same outcome measures can be computed for all participants, and there is more statistical power
for informative subgroups analysis, in subgroups created using the same selection criteria for all participants.

In addition, the proposed IPD meta-analysis has the potential to guide future research in this area. Rather than updating the analysis at regular intervals, retrospectively identifying eligible studies, we hope to be able to use it to identify knowledge gaps and generate new hypotheses, and to prospectively target research efforts at generating only the necessary data to fill these gaps or test these hypotheses. Until such a scenario is possible, consensus on core outcomes in the area of hypertensive disorders of pregnancy is necessary to enable meaningful IPD meta-analyses. We therefore invite all readers of this protocol to share their thoughts on our choice of outcome measures.

In conclusion, we believe the proposed IPD meta-analysis will provide definitive data synthesis guiding clinical practice and future research in the area of timing of delivery in women with hypertensive disorders of pregnancy at or near term.
Chapter 8

References

IPDMA in obstetrics
