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Review

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 standardisation 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.

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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) [1,2]. Hypertensive disorders of pregnancy remain one of the main causes of maternal and perinatal morbidity and mortality worldwide [3–6].

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 [7]. 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 [8,9].

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 [10].

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 post-partum haemorrhage or progression to severe hypertensive disease (systolic blood pressure ≥170 mmHg, diastolic blood pressure ≥110 mmHg, 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% versus 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 [11,12].

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 [13]. 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 [14].

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 [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