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Placental pathology and clinical trials: Histopathology data from prior and study pregnancies may improve analysis

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ABSTRACT

Placental pathology may explain adverse outcomes and reveal likely recurrent lesions. Stratifying women into intervention arms of a perinatal trial on the basis of the placental histopathological findings of the index pregnancy and evaluating the effect of the interventions against the placental findings at conclusion of a trial may enhance the trial.

The Cochrane Central Register of Controlled Trials with "obstetrics" or "perinatal" in the Title, Abstract, or Keywords published in 2015 were classified as to whether placental pathological findings from a previous pregnancy could have been used to stratify the women into the trial and placental pathology (findings) at the end of the study trial could have explained differences in the trial results, and whether these were performed.

Two hundred and twenty three of the 275 studies were not relevant. Placental pathology was an outcome measure in 2 of the remaining 52 studies. Seven trials could have benefitted by stratifying women based on previous placental pathology findings, and placental pathology findings at the end of the trial could have explained the trial results but in none of them were these performed. There were 30 trials where placental pathology could have provided an explanation for the result but review of the pathology was not undertaken in any. In the remaining 13 trials, placental pathology was unlikely to be an influence before or after the trial; however, placental pathology would have been of interest or be indicated in most of them.

Placental pathology appears to be omitted from perinatal clinical trials. Seventy-four percent (37 of 50) could have benefitted by using placental pathology results of a prior pregnancy to stratify women into intervention arms or incorporating placental pathology results in the evaluation of the interventions.

1. Introduction

The World Health Organization (WHO) defines a clinical trial as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes' [1]. In the context of perinatal trials, women may be eligible for and recruited into such trials on the basis of previous adverse neonatal or obstetric outcomes. Histopathological examination of the placenta may provide an explanation for adverse outcomes and reveal likely recurrent lesions. Therefore, it would seem reasonable to stratify women into intervention arms of a trial using the histopathological findings of the index pregnancy. In those trials where primigravid women are enrolled or where previous adverse outcomes were not a factor, analysis of the intervention effects may also benefit from placental examination.

The aims of this study were to examine how frequently findings from placental examination in a prior pregnancy were used to stratify women in perinatal trials and whether placental examination in the study pregnancy was performed to explain treatment effects.

2. Methods

The Cochrane Central Register of Controlled Trials (http://www.cochranelibrary.com/; accessed 14 Mar 2016) was searched for

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trials that had "obstetrics" or "perinatal" in the Title, Abstract, or Keywords that were published in 2015. The trials were classified as to whether (1) placental pathological findings from a previous pregnancy should have been used to stratify the women into the trial, as "yes" or "no", and, if "yes" whether that was done; (2) placental pathology (findings) at the end of the study trial could have explained differences, if any, in the trial outcomes, as "yes" or "no", and whether those were evaluated as "yes" or "no".

Stratifying a woman into a trial based on placental pathological findings from a previous pregnancy was classified as "yes" if placental pathology was relevant to the trial by way of suggested pathophysiological pathways; for example, in a trial exploring modifying maternal uteroplacental blood flow in intrauterine growth restriction, women could be stratified based on whether manifestations of uteroplacental vascular disease were found in the placenta of the preceding pregnancy. Stratifying a woman into a trial based on placental pathological findings from a previous pregnancy was classified as "no" if placental pathology was not relevant to the trial; for example, in a trial comparing using different induction methods to deliver women with prior cesarean section.

Placental pathology (findings) at the end of the study trial could have explained differences, if any, in the trial results was classified as "yes" if there was a pathophysiological link between the placenta and the outcome measure; for example, in a trial exploring modifying maternal uteroplacental blood flow in intrauterine growth restriction, it is possible that pregnancies with poor outcomes segregate into one treatment arm and are associated with uteroplacental vascular disease in the placenta. Placental pathology (findings) at the end of the study trial could have explained differences, if any, in the trial results was classified as "no" if there was no obvious pathophysiological link between the placenta and the outcome measure, for example, in a trial exploring moxibustion on correcting breech delivery.

3. Results

There were 275 studies published in 2015 listed in the Cochrane Central Register of Controlled Trials that had "obstetrics" or "perinatal" in the Title, Abstract, or Keywords. Not all the studies that were listed were actual trials in the sense of entering patients into a treatment arm to compare with either a placebo or another treatment arm. Two hundred and twenty three studies were not further analysed because they were one of the following: duplicate entry (n = 18); veterinary trial (n = 1); report of abstracts of meetings (n = 2); reviews or meta-analysis (n = 10); definitions (n = 2); assisted reproductive technology methodology (n = 5); psychosocial outcomes (n = 24); cancer outcomes (n = 6); gynaecological or gynaecology-related pharmacologic studies (n = 34); neonatal or childhood studies (n = 29); training, or technique studies (n = 22); care protocols (n = 24); pharmacokinetics or pharmacologic studies (n = 35); other miscellaneous studies (n = 11). This left 52 trial entries for which the role or usefulness of placental pathology was assessed.

In 2 studies, placental pathology was an outcome parameter, and those studies were not classified as to their stratifying or explanation status. Of the remaining 50 studies, there were 7 where both stratifying the women into the intervention arms based on prior placental pathology were considered to may have an influence on trial results and where correlating the placental pathology at the end of the study pregnancy could have provided an explanation for the trial results; in none of these 7 trials was the placental histopathology findings of the preceding pregnancy taken into account prior to randomisation of treatment or intervention. There were no trials where stratifying the women into the intervention arms based on prior placental pathology could have influenced the trial analysis. There were 30 trials where placental pathology could have provided an explanation for the trial results. In 13 trials, placental pathology was unlikely to be an influence before or after the trial. Placental histopathology was not evaluated in any of those 37 trials where the placental histopathology results at the end of the study pregnancy were considered to be helpful in explaining the pregnancy outcomes in the treatment or intervention, nor in the other remaining 13 trials (Tables 1 and 2).

4. Discussion

The placenta, being the organ at the maternal-fetal interface, can provide significant information regarding the mechanism(s) of disease in pregnancy and, through identification of lesions known to have recurrence risks, improve management of subsequent pregnancies [2–7]. Despite this, even when clinically indicated, placentas are often not sent for pathological examination [8–10]. It is, therefore, not surprising that in this study, a snap-shot of perinatal trials over a 1-year time frame, there was no integration of placental pathology in both recruitment of patients and in the evaluation of the results. This is a lost opportunity: while clinical trials, especially randomised trials, can be logistically difficult to arrange and expensive to execute [11–13], valuable information potentially can be lost by not utilising placental findings in perinatal trials.

Perinatal trials differ in their entry criteria with regard to the gravidity of the women. Lumping all multigravid women regardless of their previous placental pathology into the intervention or control arms may mask effects of the intervention being investigated. In a trial examining whether an intervention can modify a pathophysiological pathway to enable a better pregnancy outcome, for example, then both intervention (I) and control (C) arms could

Table 1
The role of placental pathology prior to trial entry and at conclusion of trial.

	n =	Number of women who were stratified on previous placental pathology findings	Number of pregnancies where placental pathology findings were evaluated against outcomes
Trial could have benefitted by stratifying women based on previous placental pathology findings, and placental pathology findings at the end of the trial could have explained trial outcomes	7	0	0
Trial could have benefitted by stratifying women based on previous placental pathology findings	0	–	–
Placental pathology findings at the end of the trial could have explained trial outcomes	30	–	0
Stratifying women based on previous placental pathology findings would not make difference to the trial, and placental pathology findings at the end of the trial unlikely to have explained trial outcomes	13	–	–