Improving the prediction and prevention of adverse pregnancy outcomes

Evidence from systematic reviews and primary studies

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Chapter 9

General discussion

In this thesis, clinically useful tools with the potential of improving pregnancy outcomes have been provided. This is achieved by providing information to clinicians and healthcare professionals to help in the triaging of care in pregnant women, which may in turn lead to a reduction in maternal and neonatal mortality or morbidity. Three different groups of women: those entering pregnancy with a pre-existing medical condition such as epilepsy; those diagnosed for the first time in pregnancy with a high-risk condition such as pre-eclampsia; and those who enter pregnancy apparently healthy, were identified for risk prediction and quantification of the magnitude of risk of complications in them and their offspring. To accomplish this, prognostic models for complications in early onset pre-eclampsia were developed and externally validated in the PREP study. In addition, the association between epilepsy and adverse obstetric complications as well as the long-term neurodevelopmental outcomes of preterm born children were quantified. The biological mechanism of a novel intervention to prevent preterm birth was also evaluated.

The key findings and implications of each chapter are:

In **Chapter 2** of this thesis, the largest pregnancy repository of individual participant data was set up for use to develop and validate pre-eclampsia prediction models, by bringing together research collaborators as part of the International Prediction of Pregnancy Complication (IPPIC) Network. As part of protocol development, primary study researchers with relevant data were identified from systematic reviews and approached to join the collaborative network, and a novel quality assessment tool was adapted and used to validate the quality of the datasets in the repository. The data was also mapped, cleaned, re-coded and harmonised ready for analysis in developing the prediction models.

As part of developing the protocol reported in **Chapter 3**, we identified and prioritised the components of the composite outcome using a Delphi survey of experts. Treatment paradox was identified as a potential source of bias, and has previously been identified as a limitation in prognostic model development. To minimise its effect, we included preterm delivery which is an effective treatment, as a component of the composite outcome, whilst management with magnesium sulphate and/or parenteral antihypertensive were incorporated as predictor variables. The analytical methods, study design and practicalities of conducting a prospective study to develop and externally validate the prediction models were presented.

Both PREP-L and PREP-S models that were developed and externally validated in **Chapter 4** to predict the risk of complications in women with early onset pre-eclampsia had good discrimination and calibration performance. The models included clinically relevant predictors used in practice to assess the severity of the disease. The performance was particularly good for the outcome by 48 hours in the PREP-S model, which makes it suitable for use as a triage tool.

The meta-analysis in **Chapter 5** provided precise estimates of the magnitude of association between epilepsy in pregnancy, anti-epileptic drugs exposure, and various adverse obstetric complications. We showed that there was a small but significant association of epilepsy in pregnancy, exposure to antiepileptic drugs and adverse pregnancy outcomes such as antepartum and post-partum haemorrhage, spontaneous miscarriage, hypertensive disorders, induction of labour, caesarean section, any preterm birth, admission to the NICU and fetal growth restriction.

Building on the work in chapter 5, **Chapter 6** reports the variation in maternal and offspring outcomes in pregnant women with epilepsy across geographical regions, economic status of countries and over time. Geographically, the Americas reported the highest rates of caesarean section, miscarriage and preterm birth, but had the lowest rate of perinatal death, whilst across time, there was a reduction in stillbirths, perinatal deaths and admission to the neonatal intensive care units, but an increase in caesarean sections.

The pilot randomised trial in **Chapter 7**, which evaluated the effects of probiotics to prevent preterm birth demonstrated the feasibility of undertaking such a study. The vaginal health of women on the oral preparation of *L rhamnosus* and *L reuteri* from early pregnancy did not improve compared to those in the control group**.**

In the meta-analysis of 64,061 children in **Chapter 8,** any degree of prematurity adversely affected the cognitive performance of children across all IQ domains, including their motor, educational and behavioural performance; the poor neurodevelopment continued into adulthood. Gestational age at birth accounted for at least 38% of the observed variance in IQ.

Women who become pregnant with pre-existing medical conditions

The systematic review and meta-analysis of the association between epilepsy and adverse obstetric complications reported in this thesis provides precise quantitative estimates of the magnitude of association between epilepsy in pregnancy, anti-epileptic drugs exposure, and various maternal and fetal outcomes. Women who become pregnant with an existing diagnosis of epilepsy have a small but significant increase in adverse pregnancy outcomes such as antepartum

and postpartum haemorrhage, spontaneous miscarriage, hypertensive disorders, induction of labour, caesarean section, any preterm birth <37 weeks and fetal growth restriction. It is therefore necessary that women with epilepsy develop a care plan with their health care provider tailored to their needs if they are considering getting pregnant as well as in the antenatal period.

Although epilepsy is one of the commonest neurological conditions affecting women of reproductive age, it is still poorly studied.[1-4] Current recommendations on the management of mothers with epilepsy are based only on a few observational studies. [5-7] The care of these women remains fragmented, with only a few UK hospital units providing joint obstetric-epilepsy care.[8] The guidelines have consistently highlighted the paucity of evidence in this area.[5-7] The findings of our meta-analysis directly led to the RCOG Green-top guideline's recommendation of regular growth-scans in pregnant women with epilepsy on anti-epileptic drugs to detect small for gestational age babies.[9]

Knowledge of the geographical variations in the rates of complication in pregnant women with epilepsy provides insight into local practices, and reflects the disparities in the distribution of health care resources in regions across the world. The rates of caesarean were consistently high in women with epilepsy regardless of the geographical region or economic rating of the country. This is despite all available guidelines recommending vaginal delivery in women with epilepsy, with the exception of women with frequent seizures.[7, 10, 11] The impact of this increase in caesarean section rate on perinatal and maternal morbidity in women with epilepsy is not known. However, obstetric complications, disability and death are linked to caesarean section, particularly in low resource settings.[12-14] Countries in the sub-Saharan region and other low

resource countries, where almost all maternal and infant mortality occur,[15] lack in research in this area, masking the true burden of epilepsy.

Apparently healthy pregnant women and those diagnosed with a high-risk condition during pregnancy

The IPPIC pre-eclampsia protocol reported in this thesis provides methods for systematically reviewing the literature to identify, validate and develop prediction models for pre-eclampsia, using individual participant data meta-analysis. By establishing the IPPIC Network along with the accompanying datasets, we have access to the largest pregnancy repository of individual participant data. This repository can be used not only for developing prediction models for pre-eclampsia as proposed in this thesis, but because it has information on other maternal and neonatal outcomes, can also be useful to researchers requiring IPD to answer other research questions.

The PREP prediction models were developed and externally validated using rigorous statistical methods to produce personalised risk estimates, which can help patients and clinicians make management decisions that are more informed. The models are based on routine tests and are readily available to clinicians. The models had good performance, and could be useful triage tools in identifying mothers for in-utero transfer to the tertiary care unit. The models also have a place in categorising women into risk groups, with low-risk women being followed-up in outpatient setting, while high-risk women can be monitored as inpatients with regular intensive monitoring. Providing this personalised risk information will allow patients the opportunity to

discuss expected outcomes with their clinicians and make decisions on place of care, intensity of monitoring or transfer to appropriate units.

Pre-eclampsia and complications arising from the condition, continues to be one of the leading causes of maternal and perinatal mortality and morbidity. An accurate way of predicting the disease and its complication, in combination with early management, may significantly improve the outcome of both mother and baby. Policymakers and clinicians are faced with difficulties in making recommendations on screening for pre-eclampsia and its complications, due to inconsistency or paucity of available evidence. As a result, current pre-eclampsia screening guidelines are based solely on maternal characteristics or history to help stratify women who may benefit from prophylactic low-dose aspirin, however these have limited predictive abilities.[16, 17] None of the guidelines acknowledge the poor performance of screening based only on maternal characteristics, nor account for the potential of more effective biomarkers such as uterine artery Doppler in improving the performance of such screening tools. Routine screening for pre-eclampsia using placental biochemical markers and uterine artery Doppler has also been shown to be cost-effective.[18]

Work coming out of the IPPIC Network for predicting pre-eclampsia using IPD will be more satisfactory in providing individually adjusted algorithms composed of a combination of screening markers to quantify a woman's risk of developing pre-eclampsia which conventional systematic reviews and meta-analysis will be unable to achieve. The advantages of an IPD meta-analysis over conventional meta-analysis are numerous, including access to previously unpublished data, flexibility in combining data from different sources and option for more

superior quality checks through contact with the study authors.[19] It also provides an opportunity to better compare multivariable prediction strategies and perform time-to-event analysis.[20]

At least 40% of spontaneous preterm birth cases are associated with intrauterine infection most commonly caused by vaginal pathogens that have replaced the normal lactobacilli, causing Bacterial Vaginosis (BV).[21, 22] Pregnant women with epilepsy and those diagnosed with pre-eclampsia are also at increased risk of preterm birth.[23-27] The pragmatic, double-blind placebo-controlled pilot trial on the effects of oral probiotic supplements on vaginal microbiota in pregnancy reported in this thesis, demonstrated feasibility of undertaking the study but did not find any difference in the rates of BV between the groups. On the contrary, the results suggests a negative effect of lactobacilli probiotics use in pregnancy on the prevalence of BV. The findings reported here are different to those previously published in this area, which formed the basis of commercial probiotic products being marketed to pregnant and non-pregnant women alike for the restoration and maintenance of a healthy vaginal flora. These findings are important because, a common pathway to preterm delivery is chorioamnionitis from ascending subclinical infection associated with changes in the vaginal microbiota,[28-30] and BV has been repeatedly shown to be an independent and important risk factor for preterm delivery.[28, 31]

Children born preterm are at high risk of cognitive deficits, learning disabilities, and behavioural and emotional problems compared to those born at term. The review reported in this thesis provides quantifiable information on the delay in cognitive development according to the severity of prematurity at birth. Although children born at extreme premature gestations are most at risk of cognitive impairment, clinicians will need to take into consideration the significant adverse effect of late prematurity on cognition. Discussions with parents on the timing of

delivery should include the long-term effects of prematurity on neurodevelopment and the magnitude of this risk. Preterm-born children diagnosed with developmental delay in early childhood therefore need consistent support in social, academic and behavioural aspects at primary and secondary school ages.

Future perspectives

Prospective studies in pregnant women with epilepsy and registries tend to focus their primary outcomes on congenital malformations and fetal harm from in-utero exposure to anti-epileptic drugs. Research is needed on other pregnancy outcomes in addition to the above, such as the long-term neurodevelopmental outcomes of children with mothers who have been exposed to different anti-epileptic drug management strategies. When developing these studies, it is important that identified core outcomes are considered for use as part of the study outcomes. There is a lack of good quality research in low-income countries, where the greatest burden of maternal and perinatal mortality and morbidity occur. These areas need to be the focus of future research to improve knowledge on the epidemiology, outcome and mortality of epilepsy in these regions, particularly in women of child bearing age, especially since most countries in these regions have the highest fertility rates in the world.[32] The relationship between seizure control in pregnancy, and anti-epileptic drugs and their dosage on pregnancy complications also needs to be evaluated. Seizure control is important during pregnancy,[9] however it is difficult to predict how pregnancy will affect seizure occurrence in pregnant women with epilepsy. Some women experiencing no change or a reduction in seizure occurrence, while others may see their seizure frequency increase or become more severe. Nearly a third of women with epilepsy continue to have seizures despite optimal medication management. The lack of consensus on the care of

pregnant women with epilepsy,[33] necessitates a seizure prediction tool capable of providing personalized and individual risk estimates to aid decision making by healthcare professionals.[34] The model should be externally validated and the generalisability as well as the clinical utility should be appropriately assessed.

Numerous prediction models have been developed for use in various obstetrics and gynaecological conditions, however very few progress beyond the development stage to be externally validated and fewer still have their impact assessed.[35] Following the development of the PREP and IPPIC pre-eclampsia prediction models, the next step would be to undertake impact assessment studies to determine whether the models do in fact make a difference to clinical outcomes. Before prediction models are implemented or integrated into clinical practice, thresholds for intervention needs to be set. Even prior to this, knowledge on whether healthcare professionals and patients to be managed with the prediction model will use or allow such models to be used on them are needed to support impact assessment studies.

Laboratory based studies have shown that different bacterial strains work in different ways,[36] and although the findings reported in this thesis suggest a negative effect of probiotics use in pregnancy on the prevalence of BV, it may be that the oral route of probiotic administration is not optimal. It is also possible that other probiotics strains may be more effective in improving vaginal health of pregnant women. Future studies could further explore these options. However, the lactobacilli preparation and administration method assessed in this thesis failed to colonise the vagina or prevent BV, and can therefore not be considered as a health technology in the primary prevention of preterm birth.

Most research on prematurity in the past have focused on those born at the more extreme end of prematurity in whom there is the highest risk of major morbidity and mortality. The evidence provided in this thesis, that late pre-term born children are at greater risk of adverse long-term neurodevelopmental delay compared to those born at term, should be taken into account by funding bodies when setting research priorities, and although considered costly, randomised controlled trials involving preterm children should plan for long-term follow-ups and standardise outcome reporting.

Finally, simple and easy to use screening tools are needed to assess and predict mild and severe long-term neurodevelopmental outcomes in preterm born children. Individual Patient Data meta-analysis should be utilised in studying the effects of factors such as antenatal and intrapartum risk factors, perinatal conditions and socioeconomic or environmental conditions in contributing to neurodevelopmental delay in addition to prematurity. The IPPIC repository reported in this thesis contains the largest cleaned, standardised and harmonised dataset of pregnancy data from researchers worldwide. This rich data source of maternal and neonatal outcomes will be a useful resource to researchers requiring IPD to answer research questions with outcomes relevant to both the mother and baby.

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