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The first trimester: Prediction and prevention of the great obstetrical syndromes

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A number of groups are currently examining the potential of screening for pre-eclampsia and gestational diabetes at 12 weeks' gestation. This can be performed at the time of combined first-trimester screening for aneuploidy using a similar method of regression analysis to combine multiple demographic and investigative factors. At present, research into the prediction of pre-eclampsia is more robust and is associated with the potential for therapeutic intervention that can reduce the prevalence of early-onset pre-eclampsia and improve maternal and neonatal outcomes.

Introduction

First-trimester screening in pregnancy has traditionally focused on the fetus: aiming to define risks of chromosomal abnormality and to identify fetuses affected by structural anomalies [1,2]. Screening for chromosomal abnormality at 11 to 13^{+6} weeks' gestation has proven to be very effective. Predictive algorithms have gradually become more complex and refined, and it is now possible to detect >90% of fetuses with Down syndrome for <5% false-positive rate [3]. The development of first-trimester screening for chromosomal abnormality has also helped clinicians

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recognize the importance of standardization of measurement for quality-assured risk analyses. The current algorithms for Down syndrome screening combine maternal history, biochemical parameters (free beta human chorionic gonadotropin (ßhCG), pregnancy-associated plasma protein A (PaPP-A) and placental growth factor (PlGF)) and biophysical parameters (ultrasound-assessed fetal nuchal translucency (NT) and nasal bone or ductus venosus flow) to assess risk [3]. The use of this combination of factors recognizes the heterogeneity of the condition being assessed, a principle that is readily transferred when developing screening tools for the great obstetric syndromes, pre-eclampsia (PET) and gestational diabetes (GDM).

Whilst maternal and infant mortalities continue to be a significant challenge in many countries, the rates of maternal and perinatal mortality are significantly lower in industrialized nations [4–6]. In this environment, it seems appropriate to review the strategic role of obstetric care and consider whether this should be expanded to include a more detailed assessment of a woman's risk of morbidity in pregnancy. Diseases such as PET and GDM not only present significant risk to mother and fetus during pregnancy but are also recognized as having a longer-term impact on maternal and infant health [7–10]. By focusing on early prediction of these conditions, it may be possible to prevent the development of symptomatic disease later in pregnancy and we hypothesize that this may be of value to not only short-term but also long-term outcomes for mother and fetus.

A number of research groups are currently attempting to develop predictive algorithms for the risk of PET and GDM. The rationale for PET screening is more clear-cut, as there are meta-analyses that demonstrate the value of early therapeutic intervention in the prevention of disease. Whilst there is currently no recognized intervention available to prevent GDM, the prevalence of this disease is increasing and early prediction may provide a means of improving the morbidity associated with this condition.

Prediction and prevention of PET

PET is recognized as one of the leading causes of maternal and perinatal mortality and morbidity, accounting for 16% of maternal deaths in industrialized nations [11]. The gestation of onset and course of this disease is unpredictable, leading, in the 1920s and 1930s, to the development of a programme for increasingly regular clinical assessment during the antenatal period [12]. Together with the use of anti-hypertensive medications and neuroprotective agents to prevent eclampsia, this has led to a significant reduction in maternal mortality in developed countries [13]. The aetiology of PET is complex and involves multiple pathways, but these can be grouped into processes related to the primary development of poor placentation and a cascade of secondary responses, which lead to the symptoms and signs of this disease [14,15]. Current surveillance and therapeutic interventions focus on responding to the second stage of this disease process. An alternative strategy would be to attempt to recognize the primary pathology at an earlier gestation, through identification of biomarkers associated with failure of trophoblast invasion, and to take steps to avoid the progression of disease.

All clinicians involved in antenatal care are aware of the risk of hypertensive disease in pregnancy and take a detailed medical history from women seeking obstetric care to try and define whether they are at risk [17]. This strategy has not proven to be useful in reducing the prevalence of disease – in part because maternal history is an ineffective screening tool but also because this assessment has often occurred too late (>16 weeks' gestation) to allow timely intervention. The majority of women who develop PET do have risk factors that will be revealed through such a booking assessment but this is not a specific enough tool to act as the reliable basis for any intervention [17]. The standard clinical assessment involves a binary approach (risk factors are either present or absent) and computerization of this, applying odds ratios to the presence or absence of each factor, improves both sensitivity and specificity [18,19]. Nevertheless, several studies have shown that screening on the basis of maternal history alone is insensitive when measured at a fixed 90% level of specificity [20,21].

The development of a more complex algorithm for first-trimester risk assessment for PET is attractive for a number of reasons. First, there is now evidence that early (<16 weeks' gestation) intervention, through the prescription of aspirin, can reduce the prevalence of *early-onset* disease [22,23]. Second, first-trimester screening for aneuploidy has led to earlier attendance for antenatal