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What are the metabolic precursors which increase the risk of pre-eclampsia and how could these be investigated further

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ABSTRACT

Several maternal and pregnancy characteristics have been associated with an increased risk of pre-eclampsia in epidemiological studies. This review discusses metabolic risk factors in particular and their interaction with other maternal and/or pregnancy characteristics. Examples of research studies that have used data from women with specific characteristics or explored the interaction between risk factors are discussed. Suggestions for future research using large data sets and incorporating knowledge of cardiovascular disease and other metabolic diseases are also highlighted.

1. Introduction

Pre-eclampsia continues to be a leading cause of maternal and neonatal mortality and morbidity affecting 3-8% of pregnancies worldwide. Exact information on the worldwide incidence of the condition and temporal changes in incidence are not available from many countries. However, data from the USA has suggested that rates have increased in recent years; 2.4% between 1987-8 to 2.9% in 2003-4 [1]. An increase was also reported in a Norwegian data set which documented rates of 3.7% between 1988 and 1992 and 4.4% between 1998 and 2002 [2]. There are many risk factors for the development of preeclampsia described in the literature, these include a prior history of gestational hypertensive disease, nulliparity, family history, obesity, pre-existing medical disease, primipaternity, assisted reproduction and short duration of sperm exposure and extremes of maternal age [3]. The metabolic health of women of reproductive age has changed over the last few decades, such that obesity is now one of the most important risk factors for the development of preeclampsia. Moreover, assisted reproductive techniques have advanced dramatically over the same time period. This review will focus on the metabolic risk factors associated with preeclampsia and discuss what is already known and suggest potential avenues for future research.

There are many cohort studies which have quantified the risk associated with the development of preeclampsia and these have recently been synthesised by Bartsch et al. [4] in a recent meta analysis in which 25,356,688 women from 40 studies in Europe and 30 studies in North America. Previous gestational hypertensive disease, chronic hypertension and antiphospholipid syndrome were demonstrated to be associated with the highest absolute risk. However, in terms of population attributable risk, obesity and nulliparity accounted for the largest population risk. Similar data have also been collated from low and middle income settings with data from 276,388 mothers and their infants analysed by investigators at the World Health Organisation [5]. The prevalence of preeclampsia/eclampsia in this study population was 4% and the odds ratio for development of the condition associated with BMI $\geq$ 35, nulliparity and chronic hypertension were 3.90 [3.52–4.33], 2.04 [1.92–2.16] and 7.75 [6.77–8.87], respectively. This study confirms that across disparate geographical locations these risk factors appear to have the greatest impact on the risk of preeclampsia.

The potential interplay between several risk factors and pre-eclampsia is illustrated in Fig. 1. Whilst the identification of risk factors for pre-eclampsia has led to numerous avenues of research and hypothesis generation, it is frustrating that these epidemiological observations, which have been very consistently reported, have not led to major breakthroughs in our understanding of the condition. Despite the consistent associations between the risk factors and the development of preeclampsia, specific causative associations remain poorly understood. The absence of a definitive

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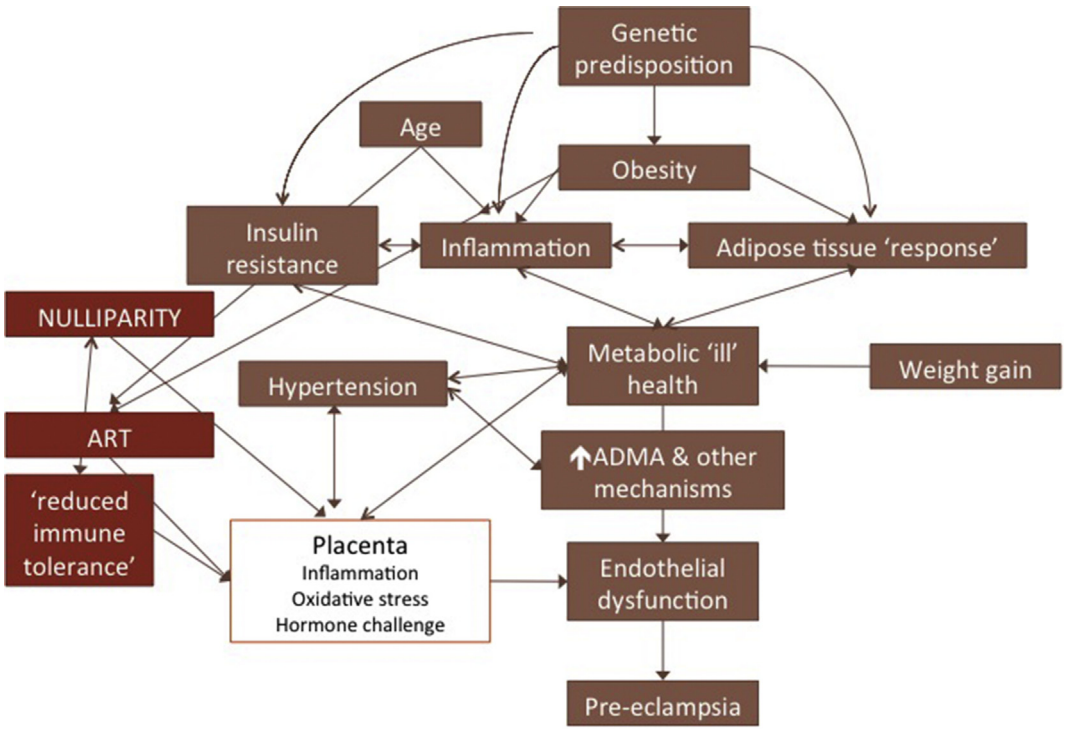

Fig. 1. Metabolic precursors for preeclampsia and their interactions. This figure illustrates the interaction between the metabolic precursors to preeclampsia and their interaction with other components of the causative pathway. The figure is not intended to be comprehensive and includes only some of the major interactions.

causative link is attributable, in part, to the fact that the number of women with any given risk factor not affected by the condition will always outweigh the number who will be affected. This was exemplified in the SCOPE cohort in which 5690 healthy nulliparous women were recruited [6]. Women with a BMI $\geq$30 kg/m^2 were twice as likely to develop preeclampsia, however the number of women with a BMI$\geq$ 30 kg/m^2 who did not develop preeclampsia outweighed those with the disease by 10:1. In addition, estimating an individual woman's risk from the epidemiological data is currently not possible from the cohort data available, as despite their frequent coexistence in clinical practice, the potential multiplicative effect of several risk factors has rarely been considered in cohort studies [4]. What can be learnt from these epidemiological risk factors, which might progress our understanding of the origins of this heterogeneous syndrome?

2. Obesity

Of the factors associated with preeclampsia obesity has been the most thoroughly studied with at least some attention to potential mechanisms. In this review it will serve as a model for the approach to understand the mechanisms associated with other risk factors.

2.1. Epidemiological considerations

The burden of obesity is increasing globally with many countries now having more than a third of adults and a fifth of adolescents classified as obese. Obesity is the leading attributable risk factor for the development of preeclampsia and appears to incur a dose-dependent relationship with the risk of developing preeclampsia with a continued increase in risk with higher categories of BMI [7]. In a large population study in Missouri, there was an incremental increase in the risk of preeclampsia with increasing BMI [8]. Whilst there was an increased risk of both early and late preeclampsia, the association between obesity and late preeclampsia was stronger. Different risks in women with equivalent BMIs have also been reported in women of different ethnicities [7].

2.2. Interaction between obesity and other biomarkers

Obesity is a risk factor for both cardiovascular disease and preeclampsia [9] and it is likely that the common risk features include components of the metabolic syndrome: hypertension, insulin resistance and dyslipidaemia [10]. In addition, obesity is likely to contribute to the pathophysiology of preeclampsia through altered inflammatory profiles [11]. It is has been estimated that around 30% of the association between preeclampsia and obesity is mediated through abnormal inflammatory profiles signified by elevated *C*-reactive protein (CRP) levels, an inflammatory mediator produced by the liver as well as adipocytes and implicated in cardiovascular morbidity [11,12]. Research studies such as the study by Bodnar et al. [11], which aimed to dissect out the key pathways relevant for the development of preeclampsia in obese women may progress the research field more quickly than studies which include women with a multitude of different risk factors. Another example of such a study was performed within the SCOPE cohort and interrogated biomarker profiles in obese women who subsequently developed preeclampsia compared to normal weight individuals [13]. A number of predictors were different between women in the different BMI groups. For example, blood pressure in early pregnancy was more strongly associated with preeclampsia in women with normal BMI than in those with obesity, in whom it was consistently raised independent of pregnancy outcome. Another key finding was that Placental growth factor (PlGF), a member of the vascular endothelial growth factor (VEGF) family, was more strongly predictive of preeclampsia in obese women who developed preeclampsia than their normal weight counterparts. In the full SCOPE cohort, low PlGF was a predictor for preeclampsia but

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