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Commentary

# Using pregnancy to assess risk and predict women's health

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The physiological state of pregnancy induces haemodynamic, metabolic and hormonal adaptations to meet the increased demands of both mother and child. This 'stress' is potentially the greatest a woman will withstand. In certain individuals, pregnancy exposes underlying genetic predispositions or vascular/metabolic susceptibility for future disease. It may instigate processes, such as direct endothelial dysfunction, which cause lasting organ damage. With enhanced health care interaction, pregnancy provides a unique opportunity for screening, modification and prevention of future diseases.

In the United States, the leading cause of female deaths is cardiovascular disease (CVD). A key meta-analysis examined the risk of future CVD in pre-eclamptic pregnancies. It demonstrated a 3.7-fold relative risk (RR) of developing hypertension 14 years postnatally, 2.2-fold RR of ischaemic heart disease 12 years postnatally, 1.8-fold RR of stroke 10 years postnatally and 1.8-fold RR of veno-thromboembolism 5 years postnatally. Mortality was increased by 49% at 14.5 years [1].

Hypertensive disorders of pregnancy (HDP) affect 10% of pregnancies and are associated with the development of CVD, obesity, hypercholesterolemia and diabetes. Women experiencing HDP and placental syndromes (PS), such as pre-eclampsia and placental infarction/abruption, are at increased risk of developing CVD both in the short and long-term. A retrospective population-based study demonstrated a 2-fold increased risk of CVD amongst women with PS alone. This was increased to 3-fold with additional impaired fetal growth [2]. Women with >1 PS have substantial risk (hazard ratio 1.43) of CVD within 5 years post-delivery. PS in combination with pre-term birth and/or small for gestational age infants increases the risk by 45% [3]. Pre-term births, miscarriages and stillbirths are all independent risk factors for developing CVD.

Gestational diabetes mellitus (GDM) occurs in approximately 10% of pregnancies. It is associated with a 7- to 20-fold increased risk of developing type 2 diabetes, as well as a 2- and 4-fold increased risk of developing hypertension/stroke and myocardial infarction respectively [4,5]. GDM is a predictor of metabolic syndrome; 27% within 11 years of delivery [6]. Moreover, children born to mothers with GDM are at increased risk of diabetes and obesity during adulthood.

Gestational weight gain (GWG) is questionably the most detrimental consequence of pregnancy on future maternal health. Excessive GWG in the first trimester is associated with impaired glucose tolerance later. Additionally, the post-partum weight of a first pregnancy can become the pre-conception weight of a second pregnancy. Therefore, inability to return to pre-pregnancy weight is a risk factor for excessive GWG during future pregnancies, as well as obesity.

Bain et al. concluded that lifestyle interventions (exercise/diet) during pregnancy were associated with reduced pre-term delivery rates, but not GDM or stillbirth rates [7]. A more structured approach with telephone sessions, web-based programs and mobile apps may be valuable. Daily aspirin prevents pre-term pre-eclampsia in high risk women [8]. Whether this intervention reduces future CVD is still the focus of long-term studies.

Undiagnosed chronic liver disease can be exposed during pregnancy and may require life-long surveillance. In Europe, pregnant women are universally screened for Human Immunodeficiency virus, Hepatitis B virus (HBV) and Hepatitis C virus (HCV). If untreated, persistent HBV infection can lead to premature mortality from cirrhosis or hepatocellular carcinoma. Vertical transmission is dependent on phase of infection and viral load. Approximately 90% of infected babies develop persistent infection; immunisation prevents this. Remarkably, considering the World Health Organisation's goal of HCV eradication by 2030, the United States does not have an antenatal screening programme for HCV.

Although common, itch during pregnancy may be a precursor to underlying liver disease. Intrahepatic cholestasis of pregnancy (ICP) affects 0.5–2% of pregnancies [9]. A small proportion of women develop ICP in association with another condition, e.g. HCV or autoimmune/cholestatic disorder. Those that present with a severe phenotype may have underlying mutations in genes that cause familial cholestasis (e.g. *ABCB4, ABCB11, ATP8B1*). Patients with pathogenic variants of *ABCB11* are at risk of ICP, whilst those with variants of *ABCB4* may develop cholangiopathy.

*Abbreviations:* CVD, cardiovascular disease; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HBV, hepatitis B virus; HCV, hepatitis C virus; HDP, hypertensive disorders of pregnancy; ICP, intrahepatic cholestasis of pregnancy; PS, placental syndromes; RR, relative risk

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**Table 1**
Opportunities for intervention in pregnancies to prevent future disease.

| Disease during pregnancy | Possible future maternal outcomes | Potential interventions during pregnancy or post-partum which require further investigation |
|---|---|---|
| **Hypertensive disorders of pregnancy** | • Chronic hypertension<br>• Ischaemic heart disease<br>• Diabetes<br>• Hypercholesterolaemia<br>• Cerebrovascular accident<br>• Veno-thromboembolism | • Aggressive risk factor management<br>• Aspirin<br>• Statins<br>• Calcium<br>• Vitamin D |
| **Gestational diabetes** | • Chronic hypertension<br>• Myocardial infarction<br>• Diabetes<br>• Metabolic syndrome<br>• Cerebrovascular accident | • Aggressive risk factor management<br>• Behavioural therapy<br>• Lifestyle intervention programmes<br>• Metformin<br>• Breastfeeding<br>• Bariatric surgery |
| **Gestational weight gain** | • Insulin resistance and diabetes<br>• Obesity | • Aggressive risk factor management<br>• Behavioural therapy<br>• Breastfeeding<br>• Bariatric surgery |
| **Viral hepatitis** | • Cirrhosis<br>• Liver transplantation<br>• Hepatocellular carcinoma | • Anti-viral therapy |
| **Intrahepatic cholestasis of pregnancy** | • Cholangiopathy<br>• Cirrhosis<br>• Liver transplantation<br>• Hepato-biliary malignancy | • Risk factor management<br>• Ursodeoxycholic Acid |
| **Renal disease** | • Chronic kidney disease<br>• Chronic hypertension<br>• End-stage renal failure | • Management of underlying disorder, e.g. lupus nephritis and immunosuppression<br>• ACE inhibitors (post-pregnancy) |

When compared to uncomplicated pregnancies, women with ICP have a 3- to 5-fold higher risk of developing future cirrhosis, hepato-biliary malignancies and gallstones. A Swedish registry study demonstrated that 15% of women with previous ICP developed significant hepato-biliary disease (hazard ratio 2.62), compared to 6% without ICP [10]. Furthermore, analysis of a Finnish birth cohort showed that 16-year-old children of mothers with ICP had increased adiposity and dyslipidaemia [9]. Although an area of interest, it has not yet been established whether ursodeoxycholic acid is protective against the development of subsequent liver disease in women with ICP.

It is beyond the scope of this commentary to focus on the full spectrum of pathologies that can present *de novo* during pregnancy, e.g. renal glomerular diseases. In addition, pre-eclampsia rates are increased in renal pathologies and may be predictive of end-stage renal disease later in life.

The development of disorders during pregnancy clearly increases the risk of disease acquisition in the years after delivery. Currently, there are few interventions during or after pregnancy which significantly impact on the risk of developing cardiovascular, metabolic, hepatic and renal disease (see Table 1). Moreover, little attention is paid to this at a policy level. Improved patient education and counseling are paramount. This needs to coincide with better interface and handover between obstetricians and other health care providers. Cost-effective screening and risk assessment tools require further development. Prospective studies may determine if early intervention prevents the occurrence of chronic diseases. Nonetheless, focus should be on prevention as this is better than cure.

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## Declaration of Competing Interest

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