Manuscript Title: The obstetrician's role in preventing cardiometabolic disease

Running title: Preventing cardiometabolic disease

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Abstract:

Key content:
Cardiovascular diseases are the leading causes of death in women and account for the majority of deaths in women living in the UK.
Pregnancy is a "stress test" for cardio-metabolic conditions, identifying women at increased risk during and after pregnancy. Antenatal and postnatal care may therefore be key times for primary and secondary prevention.
Given the growing burden of cardiometabolic diseases, pressure is mounting for integration of screening, management and preventative programs into maternity services.
This article proposes to: (i) review current knowledge around the risk of long term complications after gestational diabetes, pregnancy induced hypertension/preeclampsia; (ii) describe what preventative interventions can be done in the perinatal period and whether there is any evidence of benefit; (iii) provide practical advice for obstetricians on improving the lifelong health of women.

Learning objectives:
Be familiar with long-term consequences following gestational diabetes, hypertensive diseases of pregnancy.
Understand the evidence for interventions before and after birth to prevent future morbidity and mortality.
Recognise the important role obstetricians play in linking secondary care with primary and preventative care services to prevent cardiovascular and metabolic diseases.

Ethical issues: the role of the obstetrician in contributing to women's lifelong wellbeing

Keywords: non-communicable diseases, life-course approach, hypertensive disorders of pregnancy, preeclampsia, gestational hypertension, gestational diabetes, type 2 diabetes, hypertension, cardiovascular disease, primary prevention, secondary prevention

Introduction

Non-communicable diseases (NCDs) are responsible for the majority of premature deaths in women around the world. In the UK, cardiovascular disease (CVD) and stroke are the leading causes of death in women.[1] Risk factors for CVD, such as obesity, age, hypertension, diabetes and renal disease, are also associated with gestational diabetes mellitus (GDM) and hypertensive diseases of pregnancy (HDP), which suggests common aetiologies. The concept of pregnancy as a cardiometabolic 'stress test' is not new, i.e. the physiological changes that occur in pregnancy unmask subclinical conditions such as diabetes and hypertension (Figure 1). GDM and HDP, by definition, recede after pregnancy, but affected women remain at increased risk of type 2 diabetes (T2DM) and CVD later in life. A history of pregnancy complications, therefore, offers an opportunity to prevent cardiometabolic disease.[2] This article summarises what is known about the health consequences over the life course of pregnancies complicated by GDM or HDP, and considers the evidence available for prevention, with practical advice on how obstetricians can help to improve women's future health.

Maternal health risks after a pregnancy complicated by GDM

It was first recognised in the 1950's that women with hyperglycaemia during pregnancy were at increased risk of T2DM after birth. The first diagnostic criteria for GDM were based on oral glucose tolerance test (OGTT) values that best predicted this risk. Whilst the criteria have evolved to capture women with glycaemic levels that also place the fetus at risk,[3 4] metanalyses have consistently confirmed the observation that women with hyperglycaemia during pregnancy are at increased risk of T2DM. Although the exact magnitude of the risk varies amongst populations, [5 6] and different definitions of GDM and T2DM exist, the pooled risk of post-GDM T2DM is estimated at 7·43, 95% CI 4·79–11·51.[7] The cumulative incidence of T2DM is highest in the first 3-6 years postpartum.[8]

However, GDM is a heterogenous condition and some women are at increased risk of developing T2DM. In a metanalysis of individual risk factors, increased body mass index (BMI), non-white ethnicity, family history of T2DM, insulin use during pregnancy, high OGTT values and early gestational age at diagnosis were all associated with higher rates of converting to T2DM.[9] Maternal weight gain and birthweight did not appear to increase the risk.

Thus, as the International Diabetes Federation estimates that 1 in 6 pregnancies globally are affected by hyperglycaemia,[10] identifying women with GDM has become a priority in the fight against NCDs.

GDM and hypertension

Women with GDM are at risk of developing hypertension later in life. Evidence from a large Norwegian cohort demonstrated that, after adjusting for HDP, women with GDM have twice the risk of hypertension requiring medication within 10 years of the birth, HR 2.43 (1.91–3.10).[11]

GDM and CVD

Less commonly discussed is the link between GDM and risk of future CVD (RR 1.74, 95%CI: 1.28 to 2.35). An increased risk is also observed for coronary artery disease (RR 2.09, 95%CI: 1.56–2.80) and stroke 1.25 (95%CI: 1.07–1.48), when compared to women unaffected by GDM in pregnancy.[12] Events were more common after 10 years, highlighting that any preventative interventions for CVD will need to be sustained over many years.

Whether the risk of CVD observed in women with GDM is secondary to T2DM, as T2DM itself is a risk factor for CVD, is an important question for targeting preventative strategies. In a Canadian study of 1.5 million women, who were pregnant between 1994 and 2004 and followed for a median of 10 years, the risk of CVD was increased both amongst those with GDM who developed T2DM and those with GDM only (HR 2.82; 2.41–3.30 for GDM and T2DM; and HR 1.30; 1.07–1.59 for GDM only).[13] Interestingly, only women with GDM who developed T2DM were at increased risk of microvascular complications (including vitrectomy/photocoagulation (hazard ratio HR 4.49, 95% CI 3.90–5.17), renal dialysis (HR 7.52, 5.24–10.81), and hospitalization for foot infection (HR 4.32, 3.42–5.46)).

Maternal health risks after a pregnancy complicated by HDP

HDP and chronic hypertension

Gestational hypertension (GH) and preeclampsia (PE) affect 5-10% of pregnancies worldwide.[14] Risk factors for these two conditions show some similarities, such as obesity, older maternal age and glucose intolerance. However, PE is more likely to occur in the first pregnancy and the underlying causal pathway is more clearly linked to placental dysfunction, particularly in early-onset PE.[2]

Women who develop HDP are at risk of chronic hypertension. Women with PE have a three-fold increase in the risk of hypertension in the years following the pregnancy, pooled relative risk 3.1 (2.5–3.9).[15] In those with recurrent PE, this risk increases to six-fold.[16] The highest risk of hypertension requiring medication within 10 years of birth in women who were not known to have hypertension prior to pregnancy, occurs in those who develop preterm PE, age-adjusted HR of 14.33; 95% CI, 9.03–22.70.[11] In a Danish nationwide study of 1.5 million pregnancies, 14% of primiparous women with HDP in their 20s developed hypertension in the first decade postpartum, compared with 4% of women with a normotensive first pregnancy. The corresponding percentages for primiparous women in their 40s were 32% and 11%, respectively.[17] This group also found that the risk of hypertension was slightly higher in women with GH, compared to PE, findings that are supported by other authors and merit further investigation.[11]

HDP and T2DM

Women with HDP are at 2-3 times increased risk of T2DM compared to normotensive pregnant women.[5] [16] When GDM was a co-morbidity, the risk of developing T2DM in the 17 years after birth was

substantially greater than that with GDM alone: adjusted HR 18.49 (17.12-19.96 for GH and GDM and 15.75 (14.52-17.07) for PE and GDM.[5]

HDP and CVD

Multiple metanalyses of cohort and case-control studies have shown that PE doubles the risk of ischaemic health disease and stroke in the 10 years following pregnancy, and the risks continue long-term (Table).[15] [18] [19] It is less clear, however, to what extent HDP is causative of future CVD, or simply that these conditions share risk factors, such as obesity, age and diabetes, which favour a common aetiology (Figure 1).[20]

Interestingly, whilst preterm PE is associated with a markedly higher risk of hypertension, the metanalysis by Brown et al. failed to demonstrate that this group had more CVD events.[15] The explanation may be related to the use of different definitions of PE, the smaller number of studies reporting this outcome, and/or the long duration of follow-up required to obtain sufficient numbers of CVD events.

Although obstetricians have traditionally considered GH a benign condition as its associated maternal and perinatal outcomes are good,[21] there is increasing evidence that longer-term CVD outcomes are different. A recent longitudinal Norwegian study of over 600,000 women, using linked birth registry and CVD data, found that GH increased the risk of CVD after 14 years by a Hazard Ratio of 1.8 (95%CI, 1.7-2.0).[2] This risk increased further when GH was complicated by SGA and/or preterm birth (HR 2.6, 95%CI, 2.3-3.0).

The risk of CVD is even greater in women who develop both GDM and HDP. A recent Canadian study found that after *either* GDM or HDP (range 5 to 22-year follow-up), women had a HR of 14.7, 1.9 and 1.4 for T2DM, hypertension and CVD/death, respectively. After *both* GDM and HDP in the index pregnancy, these risks increased to 36.9, 5.7, and 2.4.[22] Additionally, there was a shorter time period between index pregnancy and development of T2DM, hypertension and/or CVD in women whose pregnancies were affected by both GDM and HDP compared to either or neither condition.

Evidence for prevention

Preventing T2DM after GDM

Interventions that have been assessed to prevent T2DM include: diet and/or exercise modification, pharmacological interventions and breast feeding.

The landmark study, the US Diabetes Prevention Program (DPP), was conducted in a group of 3234 non-diabetic, male and female adults (mean age = 51 years) with evidence of impaired glucose handling.[23] This was a three-arm randomised trial with a mean follow-up of 2.8 years, comparing placebo, metformin (850mg twice daily) and an intensive diet and exercise intervention. The incidence of T2DM was 58%

lower in the intensive lifestyle group (95% CI 48-66%) and 31% lower (17-43%) in the metformin group, compared to placebo.

There were 350 women with a history of GDM in the DPP, with a mean 12-year interval from the index pregnancy to recruitment. In a long-term follow-up study of these women conducted 10 years after the DPP,[24] women with GDM had a 48% higher risk of developing T2DM compared to those without a history of GDM. Both the intensive diet and exercise intervention and metformin were effective in reducing the risk of T2DM in women with a history of GDM (35% and 40% reductions, respectively).

Two other trials have investigated the role of pharmacological therapies to prevent T2DM in women with GDM. The TRIPOD trial compared the insulin-sensitising drug, troglitazone 400mg daily, to placebo in 266 high-risk Hispanic women within 4 years of GDM.[25] Over 30 months the study demonstrated a 55% reduction in T2DM in the troglitazone arm; however, the trial was stopped when troglitazone was withdrawn from the market. Some of the same cohort of women went on to participate in the PIPOD trial, comparing pioglitazone 35-40mg daily to placebo,[26] which showed a 62% reduction in T2DM risk; however, this drug has also been withdrawn. There is increased interest in other agents, such as the dipeptidyl peptidase 4 inhibitors, vildagliptin and sitagliptin,[25] and other insulin sensitising compounds such as myo-inositol but to date no evidence is available to support their use in clinical practice. In addition, it is debateable whether it is appropriate to prescribe such agents, probably for many years, in mostly well, asymptomatic, young women, who are likely to become pregnant again.

Several research groups have assessed the role of intensive diet and/or exercise in the postpartum period to modify the risk of T2DM in women who have had GDM.[27-30] Overall, none have demonstrated the same convincing reduction in T2DM as the DPP, although modest benefits in weight loss have been observed.[27 30 31] The first years following birth of a child are challenging for mothers and families, and lifestyle programs suffer from low recruitment and retention. Women cite competing demands on their time, as well as fatigue, practical, social, cultural, environmental and financial factors.[32]

Breast feeding is associated with a reduced incidence of T2DM following pregnancies affected by GDM.[33] Longer breast feeding (> 4 to 12 weeks) of any intensity is associated with a 50% reduction in risk by 2 years (OR 0.56, 95% CI 0.35-0.89, increasing to 78% by 5 or more years: OR 0.22, 95% CI 0.13-0.36.[33] It is possible that other factors associated with more prolonged breast feeding, such as higher level of education or lower BMI, may also be associated with a decreased risk of T2DM. Hence, further research is needed to assess these potential effects.

Preventing Hypertension and CVD after HDP

Evidence is lacking for specific screening and management programs for women who have had HDP. Advice is generally based on the same screening and preventative measures as adults with other risk

factors for CVD, e.g. smoking cessation, weight loss and exercise, control of hypertension and hypercholesterolaemia, and adoption of a DASH (Dietary approaches to stop hypertension)-like diet (emphasizing fruits, vegetables, and low-fat dairy foods; including whole grains, poultry, fish, and nuts; and containing smaller amounts of red meat, sweets, sugar-containing beverages, saturated fat, and salt than the typical Western diet).[34] A 2013 review by Berks et al,[35] extrapolating from lifestyle behaviour change intervention trials for CVD risk factors performed in a variety of settings, concluded that such interventions after HDP would be expected to reduce future CVD risk by approximately 10% (OR 0.91, IQR 0.87-0.96). However, not only has a lifestyle intervention specifically for post-HDP women not been tested in a randomised trial, but the rationale for conducting such a study is uncertain given that the exact pathways by which PE leads to CVD are not yet established.

Allowing for these uncertainties, several groups have published clinical guidelines with recommendations for screening after a pregnancy affected by PE.[36] [37] Not surprisingly, the PE definitions are varied, as are the recommendations for follow-up. NICE recommends women be made aware of the increased risks of hypertension and recurrent PE at the 6 to 8-week postnatal visit.[38] The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends: a) advising women of their recurrence risks and long-term risks after PE and GH; b), regular follow-up in primary care to monitor blood pressure (BP); c) "periodic measurement" of fasting lipids and blood sugar, and d) adopting a healthy lifestyle with maintenance of ideal weight and regular aerobic exercise.[37] ISSHP notes the lack of high-level evidence behind these recommendations and the importance of further research.

Other societies promote more structured annual cardiovascular screening. In 2013, the American College of Obstetricians and Gynecologists recommended that women with a history of preterm or recurrent PE have annual checks of BMI, BP, lipids and fasting blood glucose.[39] The expert committee, however, cautioned that this recommendation was not based on any evidence of benefit, and physicians and women need individually to balance the inconvenience and expense of annual checks with possible benefits.

An expert guideline group in the Netherlands also reviewed the literature for longer term risks in women with PE, as well as a number of other reproductive health complications.[40] They found that whilst GH, spontaneous preterm birth, small for gestational age, premature ovarian failure and PCOS are all associated with an increased risk of CVD, risk estimates for each of these conditions are all less than 2, which was below the arbitrary level selected by the guideline group to warrant additional screening. For women with PE specifically, with an estimated CVD relative risk of 2.15, the group noted the lack of randomised and prospective evidence available to support additional screening. They recommended BP follow-up for those on medication, with a full cardiovascular health check at age 50 in women with a history of PE.

In 2011, the American Heart Association (AHA) included a history of PE or GH as a marker of 'at risk' of CVD, similar to smoking, hypertension or hypercholesterolaemia.[34] In 2014, history of PE was also

included as a risk factor in the cerebrovascular guidelines for women.[41] However, other than the general lifestyle and risk factor advice recommended for all women, there were no specific changes in frequency or content of screening for CVD recommended.

Implications for the obstetrician

Our responsibility as health care professionals must extend beyond providing safe and timely delivery to encompass the implications of pregnancy complications for women's lifelong health, and by extension, the health of society. Whilst screening for CVD and diabetes largely occurs in primary care, our key role in the health system is to flag women at higher risk, thereby joining secondary and primary/preventative care. By providing accurate and informed information about the lifelong implications of pregnancy complications to colleagues, midwives, primary care physicians and women themselves, obstetricians can play an important role in primary prevention.

Women with GDM

Obstetricians can facilitate three important actions to reduce post-GDM T2DM rates. Firstly, they should promote breast feeding. There is strong evidence from a 30-year prospective cohort study that lactation duration is associated with a lower incidence of diabetes in women with and without GDM.[42]

Secondly, obstetricians should communicate to women and their primary care providers that the rate of progression to T2DM is highest within 3-6 years of GDM.[8 9] The NICE 2015 Guideline for Diabetes in Pregnancy recommends that women with GDM are all offered diet and lifestyle advice and a fasting blood glucose check between 6-13 weeks postpartum, followed by annual screening with HbA1c thereafter.[3] Ensuring compliance with postnatal testing is a challenge, with reported screening rates following GDM between 17-60% around the world.[43] In the UK, despite national guidelines, postnatal screening rates remain poor and there is a need for better strategies to improve participation. In a study of 127 primary care practices in the UK involving 2016 women with GDM, only18.5% had been screened for T2DM 6 months after birth and 20% of women attended for annual follow-up.[44] Inclusion of BP check and lipid profile testing in parallel with the recommended HbA1c particularly in those at high risk (i.e. women with increased BMI, borderline dysglycaemia, strong family history or those who needed insulin during pregnancy) should be considered in those at highest risk, although in the current fiscally constrained environment of the NHS this could be challenging. Nevertheless, advocating for a life course approach to women's health should be a priority for all health care professionals.

Thirdly, obstetricians can better utilise the numerous antenatal encounters they have with women with GDM, to provide education in a form that is individualised around each woman's longer term metabolic and cardiovascular risks, supported by practical and consistent dietary and exercise advice. The information provided should include: advice about the importance of postpartum and lifelong screening for T2DM; consistent dietary advice and goals for minimising weight gain during pregnancy and maximising

postpartum weight loss, and advice to reduce other cardiovascular risks such as smoking and a sedentary lifestyle. Some, or all of this, advice may already be given. What is important is to ensure all women receive the same high-quality, individualised care.

Since 2011 the AHA have included a history of GDM as a risk factor for CVD.[34] Evidence for specific advice to prevent CVD in this group of women, i.e. the frequency and content of cardiovascular follow-up, is lacking. As such, it is difficult to recommend actions beyond raising awareness of cardiovascular health and the importance of maintaining a healthy weight and diet, as well as a normal BP, and stopping smoking.

Women with HDP

The current advice from NICE is for practitioners to inform women who have had GH or PE that they are at increased risk of hypertension and its complications later in life.[38] Awareness of these risks amongst obstetricians may be low.[45] As a first step, therefore, raising awareness amongst clinicians through educational activities and guidelines, with practical advice for incorporating messaging about longer term risks before or after the time of birth would be helpful. Robust and clear communication strategies conveying these risks to primary care physicians will also be essential.

However, until further good-quality evidence is established in this area, it is hard to make firm recommendations regarding clinical practice in this group of otherwise well but at-risk women. One difficulty has been the lack of data as to what constitutes normal physiological measurements including BP in the early years postpartum, and how these differ after a normotensive pregnancy and one affected by HDP. Prospective studies currently underway should provide information to improve the identification of women at high risk of CVD after HDP.[46] Additionally, there are several trials planned or underway of lifestyle behaviour changes or pharmacotherapy for improving cardiovascular profiles after HDP, although at this stage they are mostly pilot in nature.

Alternative methods of screening in this high-risk population, such as community health workers/health visitors performing risk factor identification supported by digital clinical decision support tools, should be explored as potential cost effective and acceptable models for women. This approach has been used successfully in non-pregnant adults in India,[47] and it should be evaluated as a secondary prevention strategy in high-income settings such as the UK.

Conclusions

Women who develop GDM and/or HDP are at increased risk of T2DM, hypertension and CVD in later life. The obstetrician's key role is to flag these risks to women and their primary care providers and stress

the benefits of breast feeding as a preventative measure. Developing specific programs to target high-risk mothers is an important intervention, especially as they are often less likely to breast feed.

In the light of current pressures on primary care in the UK, it may be timely to consider alternative models of postpartum CVD risk assessment and support of longer-term lifestyle changes. In the USA, there have been calls for greater cooperation between obstetricians and cardiologists to identify high-risk women and initiate preventative care.[48] The AHA describe an optimal, well-woman, cardiovascular, prevention visit as including a thorough family history, screening for CVD risk factors, especially those unique to women, and lifestyle counselling.[48] The frequency at which these well-woman visits should occur depends on the presence or absence of risk factors, but the post-partum visit should be considered an opportunity to focus on lifestyle modification, such as weight management and smoking cessation, to improve cardiovascular health. In Ontario, Canada, a Maternal Health clinic has been established for women who had pregnancy complications that place them at higher cardiovascular risk.[49] The clinic aims to discuss the individualised risks of CVD, identify and modify contributing co-morbidities, encourage lifestyle changes, and facilitate longer term follow-up and/or specialist referral. To our knowledge, stand-alone models for cardiovascular or metabolic health following pregnancy have not been adopted in the NHS; however, given the immense cost of these conditions, both in the long term and in future pregnancies, this could be a model of care to consider. As discussed above, mobile digital decision support platforms could facilitate outreach models with community health workers/health visitors to improve screening rates and initiate basic preventative care measures. Whilst this may seem beyond the remit of obstetricians, lobbying for greater resources for preventative women's health is an important role we can play.

With the growing burden of NCDs, there is increased academic and clinical interest in utilising pregnancy as an opportunity to initiate preventative health actions. Obstetricians play a key role in identifying at-risk women and by connecting with primary and preventative care services, pregnancy care could be pivotal in the fight to improve women's health across the world.

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