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Title: Gestational Diabetes Mellitus: An opportunity to improve long term health in mothers and children

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Summary:

Gestational Diabetes Mellitus (GDM), the commonest medical disorder in pregnancy, is currently defined as ‘glucose intolerance resulting in hyperglycaemia that begins or is first diagnosed in pregnancy’. It is well known that GDM is associated with increased pregnancy complications as well as with long-term metabolic risks for the woman and her offspring. However, the current diagnostic and management strategies recommended by national and international guidelines are mainly focussed on short-term risks during pregnancy and delivery, except the Carpenter-Coustan criteria, which were based on the risk of future incidence of type 2 diabetes post-GDM. In this Personal View, we first summarise the recent evidence for the long-term risk for women with GDM and their offspring. Second, we suggest that a paradigm shift is needed in our thinking about GDM, moving from the perception of a short-term condition that confers increased risks of large babies to a potentially modifiable long term condition that contributes to the growing burden of childhood obesity and cardiometabolic disorders in women and their future generation. Third, we propose how we may improve current clinical practice. Finally, we outline and justify priorities for future research.

Introduction

GDM is increasingly prevalent, estimated to affect more than 20 million live births (about one in six), worldwide. Of these, more than 90% of cases are expected to occur in South and South East Asia.¹ GDM has long been a controversial diagnosis, with variations in screening procedures and diagnostic criteria internationally.²⁻⁴ In view of variations in definitions the term ‘hyperglycaemia in pregnancy’ has sometimes been used but this will include GDM, pre-gestational diabetes (pre-existing type 1 and 2) and overt diabetes diagnosed in pregnancy. Nevertheless we have known for more than 10 years that management of women with severe hyperglycaemia improves adverse pregnancy outcomes,⁵ while management of women with ‘milder degrees of hyperglycaemia’ could also reduce the rates of gestational hypertension and preeclampsia.⁶ It is also well recognised that the link between maternal glucose levels and neonatal outcomes attributed to fetal hyperinsulinemia [such as large for gestational age (LGA; birthweight >90th centile), neonatal adiposity and neonatal

hypoglycaemia] is continuous.⁷ GDM is generally perceived to be an acute condition with short-term problems for the mother and her offspring, as the glucose intolerance usually reverts to normal after pregnancy. In addition to type 2 diabetes, recent studies suggest that GDM is also a risk factor for long-term maternal and offspring cardiometabolic disease.⁸⁻¹⁰ In the knowledge that type 2 diabetes can be prevented by lifestyle intervention and weight loss of 10-15% of body weight can result in remission of type 2 diabetes,^{11,12} women with GDM and their families form a key high risk group, for whom there is a compelling case for targeted intervention.

Screening and diagnosis of GDM, in brief

While screening procedures and diagnostic criteria vary between countries, GDM is most typically diagnosed by an oral glucose tolerance test (OGTT) performed between 24 and 28 weeks of gestation.¹⁻⁴ Recent evidence suggests that the onset of GDM may occur as early as 16-20 weeks and even earlier maternal hyperglycaemia (9-10 weeks)¹³ and fetal hyperinsulinemia (14-20 weeks)¹⁴ are reported to be associated with later development of GDM and LGA. Because of this, several ongoing studies are addressing the value of screening, diagnosing and managing GDM in early pregnancy.

Who to screen and the glucose thresholds for diagnosing GDM vary across the world.¹⁻⁴ Screening strategies currently recommended/offered include: (i) universal screening using a two-step strategy (as in USA and Canada);^{15,16} (ii) selective after clinical risk factor screening (as in the UK);² (iii) universal screening by a one-step strategy in countries with 'high-risk' as well as 'low-medium risk' populations.¹⁷⁻²¹ All too frequently in many low-resource settings (e.g., Sub-Saharan Africa), testing is not routinely available partly because the OGTT is a cumbersome and labour-intensive test.²² In recognition, the American Diabetes Association (ADA) and The International Federation of Gynecology and Obstetrics (FIGO) have modified their recommendations to include either a single or two-step strategy according to the local resources.^{4,23}

Long-term implications of GDM for the mother

Among women with a previous history of GDM, the lifetime risk of type 2 diabetes may be up to 20-fold higher⁸ and nearly 50% of these women will develop abnormal glucose metabolism within 10 years of the GDM pregnancy.^{24,25} In the HAPO Follow-up Study, 52% women with GDM (defined by International Association of Diabetes in Pregnancy Study Groups [IADPSG] / WHO-2013 criteria) developed abnormal glucose metabolism compared to 20% with normal glucose tolerance in pregnancy (adjusted OR of 3.4 – 3.6) after 10-14 years of follow up.²⁵ In addition to the higher risk of diabetes, women with history of GDM also display a cluster of cardiovascular disease risk factors, such as obesity, hypertension and dyslipidaemia. This has translated into higher rates of incident ischemic heart disease in large observational cohort studies,^{8,9,26} independent of the onset of type 2 diabetes.⁹ In addition, a recent population based study from Canada showed that women with hyperglycaemia which did not reach the diagnostic thresholds for GDM, still had a cardiovascular higher risk,²⁷ although some may have met the more stringent IADPSG/WHO criteria.

Taken together, these data highlight that GDM/hyperglycaemia in pregnancy should be treated as a pre-cardiovascular disease state and that our management strategy should comprehensively identify and systematically treat cardiovascular risk factors beyond prevention of type 2 diabetes. Although the risk of incident type 2 diabetes is recognised with the incorporation of prior GDM into the QDiabetes-2018 risk prediction algorithm,²⁸ this has not been incorporated in the CVD risk calculators. Worryingly, despite this evidence, in the first year following a GDM pregnancy, only half of women in the UK underwent *any* glucose testing and an even lower proportion had their lipids measured. No real improvement in the follow-up was observed following the recent update of the NICE guidelines.⁸ In addition, women who miss postnatal testing seem to be at higher risk of CVD.²⁹ While international guidelines recommend testing for glycaemic status every one-three years,^{2,4} in real-world practice these women are often missed as they fall between primary and secondary care teams.⁸ In addition, none of these international guidelines recommend screening for other cardiovascular risk factors. Hence, a clear pathway for identifying and managing women with a previous history of GDM in the early postnatal period is needed. A simple intervention of a GDM recall register or appointment of a dedicated cardiovascular coordinator, for example, would improve the follow-up.^{30,31} Incentives

for primary care teams could be another approach as the bulk of these women will be and can be managed in the community. This should also incorporate a concerted effort for educating patients and healthcare professionals on the future risk of type 2 diabetes and cardiovascular disorders. An update of NICE and other international guidelines, recognising GDM as a pre-cardiovascular disease state is warranted.

Panel 1: Long-term complications of GDM

Complications for the women	Complications for the offspring
Hypertension ⁸	Childhood obesity ^{10,25}
Type 2 Diabetes ^{8,24,25}	Excess abdominal adiposity ³²
Vascular dysfunction ³³	Metabolic syndrome ^{34,35}
Non-Alcoholic Fatty Liver Disease ^{36,37}	Hyperinsulinaemia ³⁸
Dyslipidaemia ^{8,24,25}	Disordered glucose regulation in adolescents ²⁶
Chronic inflammation ^{33,39}	Higher blood pressure ^{40,41}
Chronic Kidney Disease ^{42,43}	Possible early onset of cardiovascular disease ⁴⁴
Ischemic Heart Disease ^{8,9}	Possible attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorders ^{41,45,46}

Long-term implications of GDM for the offspring

The combination of maternal obesity, excess gestational weight gain and GDM contributes to the development of accelerated fetal growth and accumulation of adipose tissue resulting in infants with higher birthweight that are classified as LGA.^{7,47-49} In addition, it should be recognised that excess adiposity in the offspring can be independent of birthweight.⁵⁰ The effects of LGA in GDM offspring extend well beyond the immediate concerns of birth injury and neonatal hypoglycaemia, to those of childhood obesity, the rising rate of which is a global concern.⁵¹⁻⁵³ Current estimates are that by the age of two years, one in ten children is obese and more than half will be obese by the age of 35 years.⁵⁴ This persistence of obesity into early adulthood is likely to increase the risk of type 2 diabetes and cardiovascular disease. The long-term complications in the women and their offspring following GDM are summarised in panel 1.

Early life exposures are known to influence offspring long-term health, as encompassed by the Developmental Origins of Health and Disease (DOHaD) concept. Substantial evidence from human observational studies have documented an association between exposure to maternal hyperglycaemia and obesity and disordered

glucose regulation in the children and adolescents.^{10,38,55} Such conditioning in girls could increase the propensity to GDM, thus resulting in a vicious life cycle of cardiometabolic disorders (Figure 1). Proposed mechanisms derived from studies in animals and humans include altered gene expression through epigenetic mechanisms leading to abnormal cellular signalling⁵⁶ or disturbances in the development of fetal central pathways controlling appetite and energy balance.⁵⁷

Therefore, we must seek solutions that mitigate these fetal programming effects, by developing interventions to prevent GDM among women at risk, and better management of hyperglycaemia when it develops. The approach must include optimisation of offspring cardiometabolic health to reduce the risk of childhood and adult obesity and the associated individual and population level cardiometabolic consequences.

Can we do better?

Preventing GDM

Meta-analyses of lifestyle interventions studies designed to prevent GDM showed that these can reduce hyperglycaemia, rates of GDM, gestational weight gain, and caesarean delivery, but without consistently improving perinatal outcomes.^{58,59} The same has been true for pharmacological interventions to prevent LGA.⁶⁰ However, many multi-centre studies have failed to show a reduction in GDM, perhaps because of participant failure to adhere to trial protocols, interventions starting too late in pregnancy, and/or not targeting women most at risk of developing GDM (selective screening to identify ‘at risk’ women only picks up 10-15% of those entered in the trials), or by taking a ‘one-size fits all approach’ for different ethnic groups.⁴⁹ We believe that lifestyle interventions could be effective when selectively targeted to ‘at risk’ groups. However, as detailed below, risk assessment is currently based on clinical risk alone,^{2,61} which is not sufficiently sensitive. Improving the risk stratification by developing ‘personalised, composite risk scores’ could overcome some of these barriers and allow interventions to be tested in the highest risk women. Women may also adhere better to the proposed lifestyle interventions when they feel *‘this is specifically about me’*.

Timing of screening

As outlined above, there is also growing evidence that GDM testing should be performed earlier in pregnancy. Many international guidelines recommend early pregnancy screening for undiagnosed diabetes using standard criteria.⁴ However, others advise against early pregnancy testing by plasma glucose or HbA_{1c}, even to rule out pre-existing type 2 diabetes, based on a lack of cost-effectiveness studies.² Recent data have shown that fetal overgrowth is already present when GDM is diagnosed by OGTT at 28 weeks, and by 20 weeks of gestation in women who are overweight and obese.⁶² In India, elevated fetal adiposity has also been demonstrated prior to the diagnosis of GDM, in women who did not have prediabetes or type 2 diabetes in early pregnancy (ruled out by fasting glucose).⁶³ These babies had higher adiposity but did not have elevated birthweight, the so-called 'thin-fat' phenotype.^{49,63} Although IADPSG and WHO recommend to diagnose GDM in early pregnancy using the same diagnostic threshold used at 24-28 weeks (i.e., fasting plasma glucose ≥ 5.1 mmol/l), many have not followed this due to lack of interventional evidence, clinical capacity and/or concerns about increasing medicalization of pregnancy. An ongoing randomised controlled trial identifying women by early OGTT (<20 weeks of pregnancy) will inform whether early intervention can improve pregnancy outcomes.⁶⁴ We propose, as detailed below, the need for routine detection of undiagnosed pre-existing type 2 diabetes at the antenatal booking visit to ensure that women with more severe hyperglycaemia do not remain undiagnosed until 24-28 weeks of gestation. In addition, we recommend earlier OGTT testing at 24 weeks of gestation, especially among obese women.

Personalised composite risk score based screening

To optimise the benefits of antenatal intervention, the diagnosis of GDM must be made more closely related to outcome. Prospective observational data have established that the relationship between maternal glucose and LGA is continuous, with no clear cut-point for inflection of risk.⁷ Currently many guidelines, use simple risk-scoring using some or all of the following criteria to identify women who will develop abnormal glucose tolerance, rather than GDM-related complications: BMI ≥ 30 kg/m², previous macrosomic baby weighing ≥ 4.5 kg, previous GDM, first- degree relative with diabetes, minority ethnic family origin with a high

prevalence of diabetes, polycystic ovarian syndrome (PCOS) and age ≥ 30 years. The US Department of Health also advises a simple ‘yes-no’ risk scoring to decide on who should be tested but uses age ≥ 25 years.⁶¹ These strategies do not recognise differential risk amongst ethnic groups (such as South Asians)⁶⁵ or relative risk contribution by different predictors (e.g. BMI, age, or levels of fasting and post-prandial hyperglycaemia) for outcomes (i.e. GDM or its complications) [for example, the competing risks model approach in preeclampsia].⁶⁶ In addition, the current screening strategy does not reflect the pathogenesis of GDM which is likely to be heterogeneous. Genome-wide association studies have identified candidate genetic variants which are similar between type 2 diabetes and GDM. Indeed, outside pregnancy, defects in insulin secretion (~30%) or insulin sensitivity (~50%) have been identified in women with previous hyperglycaemia in pregnancy.⁶⁷ In turn, these may also differentially contribute to the adverse effects through abnormal adipocytokines, fatty acids, triglycerides or HDL^{67,68} and/or other, currently unknown, factors. This emphasises the need to develop and evaluate personalised risk scores for diagnosis and management of GDM⁶⁹⁻⁷¹ to identify women who would most benefit from continued monitoring and intervention and those who would benefit the least (i.e., low risk). A recent study highlighted the potential benefit of using a machine learning approach to accurately predict GDM, thereby offering potential to implement prevention strategies for those at higher risk and safely reassuring those with lowest risk.⁷² While the latter data are encouraging, the applicability is limited to populations with a comprehensive health records of the previous pregnancy, including the availability of glucose challenge test (GCT) result. Nevertheless, targeting resources to those most in need is a pragmatic approach, likely to be attractive to women and health systems, all of which struggle with the demands of GDM diagnosis and management, particularly in low and middle income countries (LMICs).^{19,22}

Any new screening strategy must improve outcomes if implemented. It is clear that a diagnosis of GDM is itself associated with increased risk of intervention in clinical practice. While randomised trials demonstrate that management of GDM does not increase⁵ or reduce caesarean birth,^{5,6} implementation in a real-world setting resulted in two-fold higher rates of labour induction and caesarean birth.^{73,74}

Finally, it is probable that a contextualised approach is required. While studies are limited on the cost-effectiveness of different GDM screening strategies and diagnostic criteria,⁷⁵⁻⁷⁷ it has been debated that universal screening for GDM in the UK would be cost effective, only if the purpose were to prevent type 2 diabetes.⁷⁵ Perhaps instead of making global recommendations on cost-effectiveness, population-based, local recommendations should be considered,^{78,79} as cost-effectiveness will depend not only on the prevalence of GDM and core short-term outcomes⁸⁰⁻⁸², but also population/settings-dependent long-term outcomes for women and their offspring.

Where to go from here?

Although not possible to review all the controversies and gaps in evidence in this article, we summarise the urgent priorities for clinical practice and research and justify the rationale behind each recommendation.

Priorities for clinical practice:

1. Measure HbA1c or Fasting Plasma Glucose (FPG) in early pregnancy:
Rationale: To identify undiagnosed pre- and type 2 diabetes and improve short- and long-term outcomes. While recommended by many guidelines this is not routinely practiced, including in many high-income countries. Identifying women with severe hyperglycaemia in early pregnancy allows more time to intervene with diet, lifestyle and medication to improve their pregnancy outcomes.
2. Compulsory reporting of GDM in the maternity data systems:
Rationale: While recording of data has improved in primary care systems in many countries, the transfer-back of information by many maternity systems to primary care is lacking. Improving the accuracy of coding by including ethnicity and other key variables would enable establishment of a national register for GDM to which offspring data could be linked. This would inform development of cardiometabolic prevention programmes for women and their children.
3. Develop postnatal care pathways for women with prior GDM, prioritising them in national diabetes prevention programmes:

Rationale: Several countries including UK, Australia and USA are setting up national level diabetes prevention programmes. To expand on these, considerable resources are required even for developed countries. Prioritising women with a previous history of GDM will offer value for money, enabling better preparation for subsequent pregnancies and prevention of type 2 diabetes and cardiovascular disease. We suggest that all women with GDM have a postnatal check at around 12 weeks after birth. This could coincide with child health check or vaccination schedule in the primary care. In addition to postnatal HbA1c measurement, comprehensive cardiovascular risk factor assessment should be performed (e.g., blood pressure, smoking history and lipid management), recorded and appropriately managed.

4. Develop pathways for children born to women with GDM:

Rationale: Childhood obesity is rapidly increasing across the globe and the ‘double-burden’ of stunting and obesity is increasing in LMICs. To prevent childhood obesity, intervention has to happen at pre-school age. Health visitors and other health care professionals could be trained and provide families with advice on healthy lifestyle interventions from birth.

Priorities for research:

1. Develop and examine the utility of risk scores in early pregnancy for risk stratification of GDM and its complications, particularly in LMICs:

Rationale: Current screening strategies for detection and management of GDM are suboptimal: 1) prevalence of GDM by selective screening of ‘at risk’ women is only around 10-20% and the remaining 80-90% are negative; 2) between a third and half of all women with GDM are not identified in a recognised ‘at risk’ group and are not screened for GDM,¹ with the potential for higher risk of stillbirth.^{83,84} Obese women with a negative OGTT but who had higher HbA1c ($\geq 5.7\%$; $\geq 39\text{mmol/mol}$) at delivery have higher metabolic risk 4-years postpartum and their infants have higher risk of obesity compared to women with treated GDM;⁸⁵ 3) the current GDM screening strategies have a glucocentric approach and other novel/cardiovascular risk factors (e.g. triglycerides, adiponectin, etc) are not taken into account; 4) lifelong consequences of fetal exposure to hyperglycaemia (and other fuels) may have been already established by the time of screening; and 5) more than 90% of

GDM and 80% of maternal and infant mortality occurs in LMICs. Evidence is still lacking in many of these high risk populations, although recently completed and ongoing studies may provide some answers.^{64,86} Developing accurate, population-specific, personalised composite risk scoring has the potential to address these concerns.

2. Explore whether early pregnancy screening and intervention improves cardiometabolic outcomes for the offspring, both in the short and longer-term:
Rationale: There is little or no evidence that treating mild early pregnancy fasting hyperglycaemia reduces adverse outcomes even in the short-term. Studies focussing on short and long term outcomes are needed. There is a need to focus on the potential benefits vs. harms of early intervention. Several risk prediction models have been proposed but need to be tested and validated in different populations.
3. Find alternatives to OGTT as the diagnostic test for GDM, such as novel biomarkers or continuous glucose monitoring:
Rationale: OGTTs are difficult to perform, have poor reproducibility and are being discontinued for diabetes diagnosis beyond pregnancy. The role of emerging biomarkers, and /or continuous glucose monitoring which measure direct fetal exposure to maternal glycaemia offer alternative solutions to identify mothers and infants at risk for complications of GDM. Any such solutions should be cost effective and available in LMICs.
4. Personalised GDM management strategies for those at high- and low-risk of complications, informed by the pathogenesis of their GDM:
Rationale: Only ~20% of women with GDM have adverse pregnancy outcomes and with effective intervention, this is halved. Thus the majority of untreated GDM women do not develop adverse outcomes in pregnancy.⁵⁻⁷ Accurate identification of women who have the highest and lowest risk may enable personalised management strategies, ensuring that women at highest risk get increased attention.
5. Develop postnatal personalised risk stratification for type 2 diabetes and the associated cluster of cardiovascular risk factors to inform future monitoring of HbA_{1c}, blood pressure, and serum lipids:
Rationale: Recent evidence suggests that women with GDM are at higher risk of incident type 2 diabetes and that they develop cardiovascular disease at a

younger age. Personalised, population specific cardiovascular risk stratification will inform future monitoring and/or prevention strategies for these women with potential for better adherence in the postnatal period.

6. Understand the barriers and facilitators to improve postnatal evaluation of glycaemic and cardiovascular risk status in women with a prior history of GDM:

Rationale: Studies that can provide insights on barriers and facilitators of postnatal evaluation of cardiovascular risk status and strategies for improving them are required. Community health workers who visit and assess the children could play a role. Similarly, vaccination programmes could incorporate health checks for women with GDM. The accuracy of point of care devices for measuring HbA1c and lipid profiles have improved and could now be used for routine cardiovascular risk evaluation in community care settings.

7. Incorporate health economics into a wider range of screening and management trials and develop models of cost-effectiveness that incorporate long-term effects on mother and child, and facilitate exploration of the transferability of results between countries:

Rationale: Clinical and cost-effectiveness of the above-mentioned priorities are essential to inform policy makers across the world. This will enable countries to decide on what level of intervention(s) will be suitable for them. It is not feasible to replicate studies in all populations, especially the long-term effects. Therefore, transferability of such evidence across similar populations, will enable evidence-based guidance to be followed across many LMICs.

Conclusion:

In summary, GDM provides a unique window of opportunity to identify women and babies at increased long-term risk of obesity, type 2 diabetes and cardiovascular disease. While short-term outcomes in GDM should remain a part of the research agenda, our focus must shift towards improved earlier and more personalised diagnosis, together with the preventive care and future health of both women with a history of GDM and their offspring.

Search strategy and selection criteria:

References for this review were identified through searches on PubMed for articles published from January 1981 to Jan 2020 by use of terms, “Gestational Diabetes Mellitus”, “Hyperglycaemia in Pregnancy”, “long-term complications”, “Cardiovascular Disorders”, “offspring”, “childhood obesity” and “childhood complications”. Relevant articles resulting from these searches and relevant references cited in these articles were reviewed. Articles published in English were included. To keep the references to a minimum number, some of the original articles cited in systematic reviews were not listed.

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We, on behalf of the Diabetes in Pregnancy Working Group of the Maternal Medicine Clinical Study Group, Royal College of Obstetricians and Gynaecologist (MMCSG, RCOG), are a group of academics, clinicians and policymakers interested in the field of diabetes mellitus in pregnancy. This article was stimulated by our members' recent GDM publications that have highlighted the need for an inter-disciplinary approach to address the growing burden of GDM and its long-term sequelae that include a heightened risk of cardiometabolic disease in young women and their offspring. Our expertise is wide-ranging, from diabetes and obstetric medicine, obstetrics and fetal medicine specifically, neonatology, primary care, and public health. Our research expertise, in well- and low-resource settings, includes: mechanisms, clinical care, epidemiology, and clinical trials. Contributions to the paper by the authors are listed below.

Initiated concept of article: LAM, MAC, PvD, FD, RH, RSL, LM, CLM, HRM, DP, LP, RMR, PS, ES, SLW; Initial draft was written by PS; Editing and revision of article: LAM, AB, MAC, PvD, FD, AF, SF, JF-R, RH, RSL, LM, MM, FMM, DM, FPM, CLM, HRM, JM, DP, LP, RMR, PS, ES, NS, BT, ST, LW, SLW, CW. All authors approved the final version of the manuscript. PS is the guarantor of the article.

All authors declare no conflict of interest

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Figure legend:

Figure 1: Developmental programming and GDM; the metabolic consequences of maternal GDM may increase the risk of obesity, diabetes and cardiometabolic disorders in the child and adult, leading to a transgenerational cycle of GDM and higher cardiometabolic susceptibility.

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