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Recent updates and future perspectives on gestational diabetes mellitus: An important public health challenge

Gestational diabetes mellitus (GDM) is the most common form of dysglycemia during pregnancy. It is defined as hyperglycemia diagnosed for the first time during pregnancy, most commonly during the second or third trimester. GDM can be harmful to both the mother and the offspring. Complications to fetuses include excessive birthweight and preterm birth, while women with GDM are more susceptible to gestational hypertension, pre-eclampsia, and postpartum abnormal glucose intolerance (pAGT). Due to much debate (and confusion) over diagnostic criteria over the past decade[1], studies on the prevalence and incidence of GDM have been somewhat limited, and sometimes difficult to compare across different populations.

As a result of the rapid economic developments in recent years, the prevalence of diabetes mellitus (DM) and GDM have increased in many Asian countries[2]. Furthermore, improved healthcare awareness and the impact of GDM have also led to more screening and diagnosis, including an increasing number of countries adopting the universal screening of GDM in pregnant women. China has a large population and diverse ethnicity. People living in different provinces adopt a different lifestyle and diet. Thus, the prevalence of GDM in mainland China might differ from area to area. Previously, there have been regional studies analyzing the prevalence of GDM in mainland China, but no systematic nationwide analysis has been conducted. A recent study conducted a systemic meta-analysis on the prevalence of GDM in mainland China[3] using the 2010 International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic standard, which has subsequently been adopted by the World Health Organization (WHO) in 2013 and the International Diabetes Federation (IDF), International Federation of Gynecology and Obstetrics (FIGO) in 2015[1]. The systematic review included 25 studies from 21 regions in mainland China. Data from 79,064 participants spanning the time period from 2010 to 2017 were included, and the total incidence rate was 14.8%. Subgroup data revealed that women with a higher maternal age and weight are more susceptible to GDM. Moreover, those with a family history of DM are three times more likely to have GDM compared with those who do not, highlighting the importance of genetic factors. This study is one of the first of its kind, providing a comprehensive view of the prevalence of GDM in China. This can be crucial for strategic public health planning at the national level.

Another recent study investigated the prevalence of GDM (according to the 2014 National Health and Family Planning Commission of the People's Republic of China criteria, which is consistent with the IADPSG 2010/WHO 2013 criteria) among 78,572 pregnant women in Xiamen, China, and revealed a prevalence rate of 17.6%[4]. The minor difference in prevalence estimates between this and the earlier mentioned study may be attributed to regional, ethnic, dietary, and lifestyle differences. Results from the subgroup analysis in this study is similar to that in the systematic review, with the incidence rate higher among pregnant women with a higher maternal age, BMI, and a family history of diabetes or hypertension. These results further highlight maternal age, weight gain in early pregnancy and systolic blood pressure as important determinants of GDM.

Gestational diabetes mellitus can lead to metabolic complications in both the mother and the offspring. Therefore, prevention, earlier identification, and treatment in clinical practice are especially important. There have been many studies that have investigated the effectiveness of using conventional risk markers such as age, weight, family history, etc. for the prediction of GDM. However, no risk scores have been universally accepted for use in different populations. Some other biomarkers being proposed include body mass index (BMI), hemoglobin A1c (HbA1C), and different hormones, but these factors alone are not sufficiently strong to provide a robust prediction of GDM. A recent study from Japan aimed to identify new predictive biomarkers for GDM using a metabolomic approach[5]. Levels of metabolites in serum and urine samples of 121 participants with GDM were analyzed using hydrophilic interaction chromatography tandem mass spectrometry. Their samples were then compared with that of the control group. The investigators identified three metabolites, namely glutamine in serum, and ethanolamine and 1,3-diphosphoglycerate in the urine, which are associated with the risk of GDM. When combined, the panel of biomarkers had an area under the receiver operating characteristic curves of >0.8. The metabolites identified in urine could play an important role in amino acid metabolism and the pentose phosphate pathway and relate to subsequent GDM, but the exact relationship between the metabolites, metabolic

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pathways, and the pathogenesis of GDM still remains unclear. Nonetheless, with more research and independent validation, this new metabolomic approach could open a new avenue in predicting GDM accurately and, thus making early prevention possible. It is also important to note that metabolomic markers among subjects with GDM of different ethnicities may differ, as well as according to the underlying pathophysiology of GDM. Therefore, much work remains to be done to identify biomarkers predictive of GDM, including a systematic comparison with established risk factors.

There has been a long-standing debate on the diagnostic criteria of GDM, though it appears that a consensus is finally emerging, with most national and international guidelines now adopting the 2010 IADPSG criteria for diagnosis[1]. Other factors such as at what gestational age the test is taken can also affect the diagnostic results. At <24 weeks, the IAPDSG criteria do not recommend performing a 75 g oral glucose tolerance test (OGTT), due to insufficient data regarding thresholds[6]. Instead, the IADPSG defines a fasting plasma glucose of 92–125 mg/dL (5.1–7.0 mmol/L) at <24 weeks as diagnostic of GDM. At 24–28 weeks gestation, a 75 g OGTT is performed and GDM is defined when at least one of the following three values are met: fasting plasma glucose (PG) level 92–125 mg/dL, 1 h PG level ≥180 mg/dL (10.0 mmol/L), 2 h PG level ≥153 mg/dL (8.5mmol/L)[6]. The 2010 Japanese Society of Obstetrics and Gynecology (JSOG) criteria has adopted these diagnostic thresholds for OGTT, regardless of gestational age. It states that GDM is defined when at least one of the following three values is met at any gestational age: fasting PG level 92–125 mg/dL, 1 h PG level ≥180 mg/dL (10.0 mmol/L), 2 h PG level ≥153 mg/dL (8.5mmol/L). A recent study conducted in Japan examined how the gestational age at the time of the 75 g OGTT could affect the prevalence of GDM[7]. The study compared 2,578 pregnant women according to the timing of their OGTT, into three groups: <14 weeks, 14–23 weeks, and 24–32 weeks. The results indicated that fasting glucose was higher among the early OGTT group (<14 weeks), and participants had higher chances of being diagnosed with GDM based on the 2010 JSOG criteria if they had undergone a 75 g OGTT at <14 weeks gestation compared with those who had undergone the test at 24–32 weeks gestation (adjusted odds ratio 1.25, 95% confidence interval 1.07–1.46). On the other hand, based on the 2010 IADPSG criteria, women whose fasting PG levels were examined at <24 weeks had a lower chance of being diagnosed with GDM than those who did a 75 g OGTT at 24–28 weeks gestation. Several previous studies highlighted that fasting PG levels, 1 h and 2 h PG levels at 75 g OGTT all change during pregnancy depending on the gestational age. Therefore, applying the same threshold to diagnose GDM at earlier gestational age might not be accurate. More studies are required in order to evaluate what would be appropriate cut-off values for the 75 g OGTT should it be implemented earlier in pregnancy, and the potential implications of earlier screening and earlier intervention.

Gestational diabetes mellitus is associated with long term metabolic disorders in the mother. In particular, women with GDM are at substantially increased risk of type 2 diabetes[8]. Thus, follow-up is recommended for those who had a history of GDM. A long-term study was conducted in Hong Kong to determine the maternal cardiometabolic outcomes 22 years after GDM diagnosis (by WHO 1999 criteria)[9]. Eighty participants with normal glucose tolerance (NGT) during pregnancy and 38 others with GDM/gestational impaired glucose tolerance (GIGT) completed the 22 years follow up. At 8 years postpartum, 40.3% of those in the GDM/GIGT group developed pAGT. The percentage increases to approximately 53% at 22 years postpartum. At the same time, for the NGT group, the percentage of the group having pAGT later on also increased from 17.7% at 8 years postpartum to 30% at 22 years postpartum. Remarkably, the fasting and 2 h glucose values during OGTT in pregnancy were associated with different glucose parameters and total glucose area under the curve at OGTT 22 years later. Those with a GDM/GIGT history had lower indices of β-cell function at OGTT at both 8 and 15 years postpartum, highlighting the role of impaired β-cell function.

The identification of risk factors for postpartum abnormal glucose tolerance (pAGT) could help to identify those who have a high risk of developing pAGT, and facilitate the implementation of measures such as dietary and lifestyle changes to prevent the onset of pAGT after pregnancy. A recent study analyzed the clinical and genetic characteristics of 213 Japanese women who had a recent history of GDM, and determined how these characteristics were associated with pAGT[10]. In this study cohort, the prevalence of pAGT was 28% on OGTT at a median 24.9 weeks postpartum. As aforementioned, the 2010 IADPSG criteria could be used to diagnose GDM based on the three threshold values of 75 g OGTT. Results from this study showed that among the 142 women who had a single abnormal OGTT value, 33 of them (23.2%) had pAGT. This indicated that even for patients who had a relatively less severe case of GDM with only one abnormal value during OGTT, the risks of pAGT should not be overlooked. The study identified four metabolic parameters from the antepartum OGTT profile that could serve as antenatal predictors of pAGT, including 1 h PG, 2 h PG, insulinogenic index (IGI) and insulin secretion-sensitivity index-2 (ISSI-2). The IGI in the pAGT group was significantly lower than that in the normal glucose tolerance (NGT) group, highlighting the relationship between impaired β-cell function and a later risk of pAGT. The other three parameters are also closely related to β -cell capacity for insulin secretion. Additionally, the genotyping of single-nucleotide polymorphism (SNPs) at 45 type 2 diabetes susceptibility loci were conducted to investigate the relationship between these candidate genetic variants and pAGT. Four SNPs showed a nominally significant association with the

occurrence of pAGT, including rs266729 (*ADIPOQ*), rs6017317 (*HNF4A*), rs5215 (*KCNJ11*), and rs7177055 (*HMG20A*). A genetic risk score of 0–8 was constructed according to the number of risk alleles each individual carried at these four SNPs. The risk of pAGT increased according to the number of risk alleles (OR 1.91, 95% CI 1.40–2.61, $P = 0.00005$). Of note, three of the four aforementioned candidate genes were related to insulin-secretion, highlighting the link between impaired insulin secretion and pAGT. Although there is much ongoing work exploring how to improve the prediction of pAGT, this study demonstrated the potential to utilize clinical characteristics and genetic markers to predict future pAGT.

Although GDM represents the main form of hyperglycemia in pregnancy, glucokinase-maturity-onset diabetes of the young (GCK-MODY) is another form of hyperglycemia caused by inherited mutations in the glucokinase gene. Generally, complications are rare and medical treatments are seldom needed, except for pregnant women with GCK-MODY because the disorder may affect the offspring, resulting in perinatal complications. A recent study analyzed the pregnancy outcome of Japanese patients with GCK-MODY, who were treated with either insulin injections or diet intervention during pregnancy. The study revealed that for the unaffected offspring born to an affected mother, insulin treatment would result in a lower birthweight (3025 g vs 3593 g)[11]. For affected offspring born to affected mothers, birthweight was also lower in the insulin-treated group (2532 g vs 2800 g). Importantly, perinatal complications, including small-for-gestational age, occurred only among affected offspring born to insulin-treated mothers. The authors therefore do not recommend routine insulin treatment in mothers with GCK-MODY during pregnancy, and suggest close monitoring with serial ultrasound to monitor fetal growth remains an appropriate way to approach GCK-MODY during pregnancy.

The present article highlights some findings from recent studies on GDM, especially from the pages of *Journal of Diabetes Investigation* (JDI). The large burden of GDM, whereby more than 1 in every 10 pregnancies in the region are affected, will present significant public health challenge to most countries. Some of the challenges and key research questions relating to GDM are summarized in Figure 1. Given the large burden and significant long-term consequences to the mother and offspring, strategies to

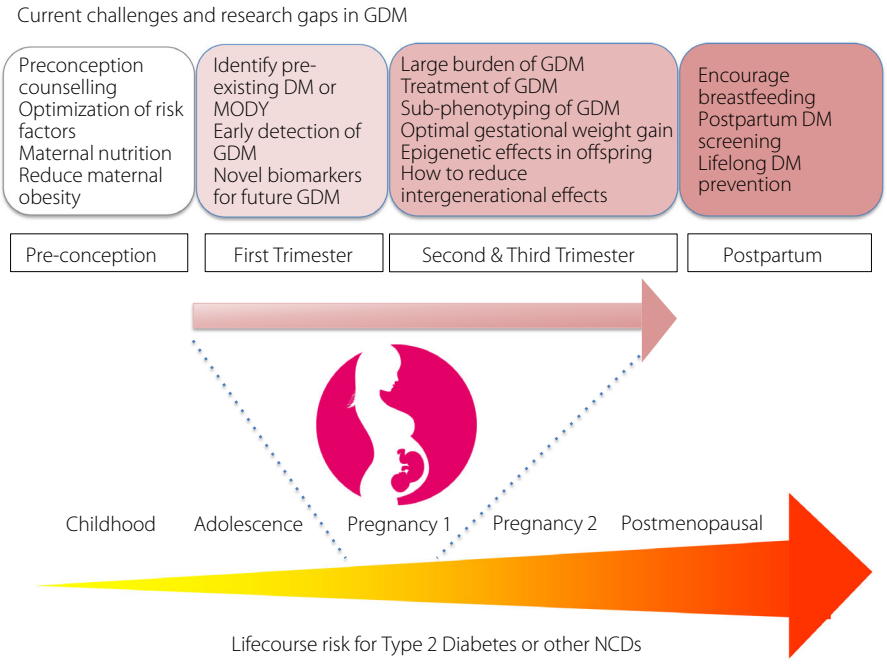

Figure 1 | Current challenges and research gaps in relation to gestational diabetes. Whilst pregnancy only represents a short time window in the life course of a woman, it represents a particularly important window of opportunity to address the risk of diabetes and other NCDs, especially among women affected by gestational diabetes mellitus. Some of the current challenges and research gaps in GDM are highlighted according to the different stages of pregnancy. The schematic diagram of the pregnant mother with the fetus highlights the potential for intergenerational effects on the future risk of diabetes and obesity in offspring of mothers with GDM. There is much that can be achieved post-partum, including the need to encourage breastfeeding, to remind mothers to undergo a postpartum oral glucose tolerance test (OGTT), followed by subsequent periodic testing for dysglycemia, and efforts in diabetes prevention given the increased risk of diabetes among women with a history of GDM. GDM, gestational diabetes mellitus; DM, diabetes mellitus; MODY, maturity-onset diabetes of the young; NCDs, non-communicable diseases. Pregnancy 1, first pregnancy; Pregnancy 2, second pregnancy.

identify at-risk individuals early, and to implement intervention to reduce the associated complications, seem warranted but require formal evaluation in clinical trial settings. Reducing hyperglycemia in pregnancy may also have beneficial effects on reducing the intergenerational effects on the risk of obesity and diabetes in the offspring. Some biomarkers such as metabolomic markers are emerging as promising candidates to facilitate the identification of individuals at risk of GDM. Given the increased risk of diabetes and other non-communicable diseases later in the life course in women with GDM, how to improve postpartum screening, and engage women to reduce future progression to pAGT and cardiovascular disease are most important, with a significant public health impact.

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DISCLOSURE

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