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The interplay between maternal obesity and gestational diabetes mellitus

Abstract: There is a strong epidemiological association between maternal obesity and gestational diabetes mellitus (GDM). Since the publication of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study on women with mild hyperglycemia in 2008, new criteria have been introduced in maternity services internationally for the diagnosis of GDM. As a result, the diagnosis of GDM may be made in one-third of obese women (n=68). The aim of this review was to examine the interplay between maternal obesity and GDM in light of the HAPO study and the subsequent revised diagnostic criteria. Obesity and GDM are important obstetric risk factors because they both are potentially modifiable. However, the new international criteria for the diagnosis of GDM have serious resource implications for maternity services provided to the large number of women attending for care in developed countries. Further consideration needs to be given as to whether obese women with mild hyperglycemia need to be referred to a multidisciplinary team antenatally if they do not require insulin treatment.

Keywords: Diabetes mellitus; gestational diabetes; hyperglycemia; obesity.

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Introduction

Maternal obesity in early pregnancy is an important risk factor for gestational diabetes mellitus (GDM) [1]. Moreover, epidemiological studies show that both conditions

are common and their prevalence is increasing, both are associated with increased fetomaternal complications, both have potentially lifelong consequences for a woman and her offspring and, accordingly, both consume increasing healthcare resources [1–3]. Yet, there is little consensus about the diagnosis and management of GDM which is associated with remarkable variations in obstetric care [4].

Diagnosis of gestational diabetes mellitus

GDM may be defined as “any degree of glucose intolerance with onset or first recognition during pregnancy” [5]. This definition includes women with “overt” or type 2 diabetes mellitus (T2DM), who present for the first time during pregnancy. Others confine the diagnosis of GDM to onset or first recognition during pregnancy but with a return to normal glycemia after birth [6]. The original criteria for the diagnosis of GDM using a three-hour 100 g oral glucose tolerance test (OGTT) were chosen to identify women at high risk of developing T2DM after pregnancy and were derived from criteria used for non-pregnant subjects [7]. However, the original criteria used for the diagnosis of GDM based on the OGTT values were determined by the woman's risk of developing T2DM outside pregnancy and were not determined by an increased pregnancy risk for her or her baby [7].

The findings from the recent Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study led to recommendations lowering the threshold for the diagnosis of GDM. The American Diabetes Association (ADA), in their most recent recommendations, concluded that evidence was not strong enough to demonstrate superiority of either a one-step 75 g OGTT or a two-step approach [8]. Using a 75 g OGTT the criteria also allowed for the diagnosis to be made based on a single abnormal result. The European Association for the Study of Diabetes and the World Health Organization (WHO) support a 75 g OGTT but, until recently, used different diagnostic thresholds [8–10].

In 2010, WHO convened an expert international group to review their recommendations on GDM in the light of

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the recommendations arising out of the HAPO study [10]. It acknowledged that its 1999 recommendations were not evidence based, were more than 10 years old and needed to be updated. A new systematic review was conducted using databases (up to February 2012), which focused on short-term pregnancy and perinatal outcomes. Potential risks of treatment, other than premature delivery, and potential long-term benefits were not evaluated. The systematic review found that whether the International Association of Diabetes and Pregnancy Study Groups (IADPSG) or the 1990 WHO criteria for GDM were used, GDM was associated with an increased risk ratio (RR) of large-for-gestational age (LGA) (RR 1.73 for IADPSG, RR 1.53 for WHO) and with an increased risk of pre-eclampsia (RR 1.71 for IADPSG, RR 1.69 for WHO). Both sets of criteria found an increased risk of cesarean section (CS) and shoulder dystocia with GDM, but the evidence was weak.

It should be noted that while the WHO review found an association between adverse outcomes and severe hyperglycemia, the association was weaker for mild hyperglycemia. Using a simulation model, the adoption of the new IADPSG criteria would reduce the incidence of LGA by only 0.32%, pre-eclampsia by 0.12% and would have no impact on CS rates [11].

The WHO review made three recommendations:

1. Hyperglycemia first detected at any time during pregnancy should be classified as either:
 - Diabetes mellitus (DM) in pregnancy
 - Gestational diabetes mellitus.
2. Diabetes mellitus in pregnancy (DMIP) should be diagnosed by the 2006 WHO criteria for diabetes if one or more of the following criteria are met:
 - Fasting plasma glucose ≥ 11.1 mmol/L (126 mg/dL)
 - Three-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load
 - Random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) in the presence of diabetes symptoms.

There are no established criteria for the diagnosis of diabetes based on the one-hour post-load value.

3. The diagnosis of GDM at any time during pregnancy should be based on one of the following values:
 - Fasting plasma glucose = 5.1–6.9 mmol/L (92–125 mg/dL)
 - One-hour post-75 g oral glucose load ≥ 10.0 mmol/L (180 mg/dL)
 - Two-hour post-75 g oral glucose load 8.5–11.0 mmol/L (153–199 mg/dL).

This distinction between DMIP and GDM is new and categorizes maternal hyperglycemia according to severity. WHO has decided to adopt the IADPSG/HAPO criteria for

GDM in the interests of universal consensus. The definition of GDM applies at any time during pregnancy. The WHO review also acknowledged that implementing the new recommendations has resource implications, but that any decisions about resources should be made locally.

Screening for GDM during pregnancy, however, varies worldwide. In the United States, it is recommended that all women should be screened using a 50 g challenge one-hour OGTT at 24–28 weeks of gestation [9]. Early screening should also be undertaken in women with a history of impaired glucose metabolism or GDM in a previous pregnancy and in women with a body mass index (BMI) >29.9 kg/m² [9]. The IADPSG recommended the 75 g two-hour OGTT at 24–28 weeks and that consideration should be given to screening women at high risk of T2DM with a fasting or random plasma glucose sample at the initial antenatal visit. In Europe, women are screened selectively based on risk factors [8].

The prevalence of GDM reported varies widely, for example, from 1% to 26% in the United States [3]. The American College of Obstetrics and Gynecology (ACOG) estimates that up to 6%–7% of pregnancies are complicated by DM and that 90% of the cases are due to GDM [9]. A review of 23 European countries identified 32 estimates of GDM and found that the prevalence was 2%–6% in more than half of the reported studies [8]. It should be noted that most of the European studies used a 100 g OGTT. After excluding 1.8% with more severe hyperglycemia, 16.1% of women in the HAPO study were diagnosed with GDM post-hoc giving an average of 17.9% in the 15 centers [12].

The wide variations in the prevalence of GDM are due to differences in the type of OGTT used, in the diagnostic criteria used, in the gestational age at screening, in ethnicity and obesity levels of the study population, and whether the screening is universal or selective. It also may be difficult to distinguish between cases of preexisting or overt T2DM and GDM, particularly as many women do not have an OGTT performed postnatally to determine whether they remain glucose intolerant or not [13].

HAPO and gestational diabetes mellitus

The HAPO study examined the relationship between mild hyperglycemia in the third trimester, using a 75 g OGTT (in the absence of GDM as previously diagnosed), and perinatal outcomes in a heterogeneous, multinational, multicultural ethnically diverse cohort of 25,505 pregnant women. The primary outcomes were birth weight (BW) $>90^{\text{th}}$

centile, primary CS, clinically defined neonatal hypoglycemia and a cord C-peptide >90th centile (Table 1).

The IADPSG Consensus Panel established after publication of the HAPO study recommended that OGTTs should be performed between 24 and 28 weeks of gestation [14]. The HAPO study was intended to exclude women with overt DM [15]. However, the panel also noted that women with preexisting or overt T2DM currently may not be diagnosed until they become pregnant and that the problem may increase in magnitude if obesity rates in young women increase. It also recommended universal early testing in populations with a high prevalence of T2DM, especially if metabolic testing is not commonly performed in this age group before pregnancy.

In defining increased risk with mild hyperglycemia, the IADPSG Consensus Panel concluded that the predefined value for this odds ratio (OR) at the threshold relative to the mean should be 1.75 for any of the fasting, one-hour or two-hour plasma glucoses of the cohort. Notably, 1.7% were already unblinded at field centers because of severe hyperglycemia [16]. Of the remaining subjects, the diagnosis of GDM was made on the fasting glucose in 8.3% of cases, the one-hour glucose in an additional 5.7% and the two-hour glucose in another 2.1% [14]. The importance of the fasting glucose, however, varied three-fold in HAPO between Barbados and Thailand.

A number of observations can be made about the HAPO study. There was wide variation in the primary pregnancy outcomes between the study centers (Table 2). The primary outcome of neonatal hypoglycemia was based on a notation in the medical records and not on the measurement of neonatal glucose in all cases, which may explain the wide 0.3%–6.4% range between centers. The variation may also be explained by the percentage of samples in individual field centers where the cord glucose was not processed quickly within the required time [16].

The primary outcome of primary CS was 17.7% and varied between 8.6% and 23.5%. There was no information provided on the indication whether it was elective or emergency and what was the influence of parity. The primary outcome of LGA depends on accurate

Table 1 Incidence of primary outcomes in the HAPO study.

Primary cesarean section (n=3731)	16.0% (range 8.6%–23.5%)
Neonatal hyperglycemia (n=480)	2.1% (range 0.3%–6.4%)
Cord C-peptide >90 th centile (n=1671)	8.4% (range 5.9%–15.1%)
Birth weight >90 th centile (n=2221)	9.5% (range 9.0%–9.9%)

HAPO=Hyperglycemia and Adverse Pregnancy Outcome.

Table 2 Odds ratios for fasting plasma glucose and primary outcomes (as a continuous variable) in the HAPO study.

Primary cesarean section	1.11 (1.06–1.15)
Birth weight >90 th centile (n=2221)	1.39 (1.32–1.44)
Neonatal hyperglycemia (n=480)	1.08 (0.98–1.19)
Cord C-peptide >90 th centile (n=1671)	1.55 (1.47–1.64)

HAPO=Hyperglycemia and Adverse Pregnancy Outcome.

sonographic dating across all centers. The incidence of LGA in the study cohorts was 9.5% rather than the expected 9.9%. LGA is more likely due to other causes than maternal hyperglycemia, and thus, treatment of mild hyperglycemia in the third trimester may have little impact on excessive fetal growth and the associated obstetric complications, such as shoulder dystocia and brachial plexus injury. C-peptide is produced in equal amounts to insulin and is considered a good measure of endogenous insulin secretion [17]. Its half-life is longer than insulin and it circulates at concentrations approximately five times higher in the systemic circulation. In the HAPO study, cord bloods collected at delivery were analyzed at a central laboratory using a radioimmunoassay for serum C-peptide. Results were available for 85.3% of participants and the mean value was 1.0 µg/L (SD 0.6) with a range of means among centers of 0.9–1.2. Among field centers, the range of cord C-peptides >90th centile ranged from 5.9% to 15.1%.

There was a strong association between cord blood C-peptide >90th centile and increasing maternal glycemia with an OR of 7.65 (CI 5.17–11.32) for the highest category of the fasting plasma glucose. The C-peptide >90th centile OR was 7.65 for fasting glucose, 4.65 for the one-hour glucose and 3.43 for the two-hour glucose. It is also notable that the OR of 7.65 for fasting glucose compares with the OR of 5.01 for BW >90th centile, 1.98 for clinical neonatal hyperglycemia and 1.60 for primary CS. Therefore, fasting maternal glucose at the OGTT had the strongest association with cord C-peptide. On average, maternal glucose was measured 11 weeks before collection of cord blood C-peptides [18]. The relationship of cord C-peptide was much stronger with neonatal adiposity than maternal glucose whether it was fasting, one-hour or two-hour glucose, and no one glucose measurement was superior to the others. It is interesting that a fasting glucose at the time of OGTT had the strongest association with measures of neonatal adiposity. This raises the possibility that metabolic factors other than maternal hyperglycemia such as hypertriglyceridemia may be influencing neonatal adiposity.

The HAPO study and the subsequent response remain controversial [3, 19]. It has been pointed out, for example, that the senior HAPO investigators were also the authors of the IADPSG consensus document, that an OR of 1.75 was chosen arbitrarily and that the reproducibility of the IADPSG criteria is unknown [19]. The revised WHO recommendations, however, offer an opportunity to review the models of care for women diagnosed with GDM during pregnancy. It may not be necessary with women diagnosed with GDM, using the more sensitive IADPSG criteria, to receive the intensive fetal and maternal monitoring that women diagnosed with GDM previously received and that women with T1DM or T2DM should continue to receive.

Maternal obesity and GDM

These new post-HAPO circumstances raise new questions about the relationship between maternal obesity and glycemic control. The relationship between maternal BMI and hyperglycemia, however, is poorly characterized because BMI has not been calculated accurately in early pregnancy, and the definition of GDM has varied over time and between studies. Further research is urgently required because the numbers of pregnant women affected are very large. It may be that all women with obesity should be screened as usual for GDM at 24–28 weeks of gestation but that women with class 2 (BMI 35.0–35.9 kg/m²) and class 3 (BMI 40.0–44.9 kg/m²) obesity should be screened for DM soon after their first antenatal visit [20].

There is also uncertainty about the role of inflammatory biomarkers in the interplay between maternal obesity and GDM. There are associations between inflammatory biomarkers and both obesity and GDM, but it is difficult to tease out whether inflammation in obese women contributes to the development of GDM or whether abnormal inflammatory biomarkers reflect simply an epidemiological association [21]. In obese women, there are uncertainties about the role of hyperglycemia in programming intrauterine fetal growth development and whether other metabolic abnormalities, such as hypertriglyceridemia, may be more important.

It should also be noted that the association between GDM and LGA, pre-eclampsia and CS in women with milder forms of hyperglycemia may be influenced by maternal BMI.

There is also no evidence that rates of LGA or fetal macrosomia are increasing in developed countries despite increasing rates of obesity and GDM [22].

HAPO and maternal obesity

In a secondary analysis of the HAPO study, both maternal GDM and obesity were independently associated with adverse pregnancy outcomes [12]. The definition of GDM used was the revised definition recommended post-HAPO, and it should be noted that 2.9% (n=746) were excluded because of glucose unblinding and 5.5% (n=412) were excluded primarily because they had undergone glucose testing or delivery outside the HAPO study.

It is also notable that not only was the diagnosis of obesity not made until the time of the OGTT but the categorization of obesity was also based on a BMI ≥ 33.0 kg/m² and not the WHO standard >30.0 [5]. To take into account weight gain during pregnancy, the researchers based their arbitrary re-categorization on regression of the BMI at OGTT on prepregnancy BMI and gestational age at the OGTT. This, of course, assumed that weight gain in pregnancy is linear and does not make allowance for the wide variation in the gestational ages at which the OGTT was performed. The arbitrary obese categories were compared with a BMI <22.6 kg/m² at the time of the OGTT and not the WHO standard of a normal BMI 20.0–24.9 kg/m².

With respect to the outcomes, the OR for the different statistical models found that the associations with GDM were consistently stronger than the associations with obesity at the OGTT. Indeed, there was no association between obesity alone and shoulder dystocia/birth injury despite obesity alone being associated with OR of 1.7 (CI 1.5–2.0) for BW $>90^{\text{th}}$ centile and an OR of 1.7 (CI 0.4–1.9) for neonatal body fat $>90^{\text{th}}$ percentile. This is consistent with a previous meta-analysis which found no relationship between maternal obesity and shoulder dystocia [23].

While the authors recommended that obese women with or without GDM should follow the Institute of Medicine guidelines and avoid excessive gestational weight gain (GWG), obese women already gain less weight than non-obese women [24]. The modest increase in OR for certain outcomes with obesity alone may be attributable to genetic influences, and interventions during pregnancy in obese women without GDM may not lead to improved clinical outcomes.

The categorization of maternal obesity

While there are challenges in the diagnosis of GDM, there are also challenges in the classification of maternal obesity [25]. The diagnosis is usually based on the WHO

categorization of BMI which is only a surrogate measure of adiposity and provides no information on the distribution of adiposity. There may also be considerable variations in adiposity in different ethnic groups at the same BMI measurement [26]. This explains why GDM is more common in certain ethnic groups.

Furthermore, most epidemiological studies base the calculation of BMI on self-reported weight and height, which leads to 22% of pregnant women being assigned to the wrong BMI category and the diagnosis of maternal obesity being missed in 5% of cases [27]. In a Canadian study ($n=2667$), outside of pregnancy, screening for T2DM based on self-reporting of BMI led to an exaggerated risk in obese subjects because subjects who were mildly obese reported themselves as non-obese [28].

This is particularly important in countries where maternal obesity is an indication for selective screening for GDM. The timing of BMI calculation matters, and ideally should take place before 18 weeks of gestation [4]. Many epidemiological studies use prepregnancy self-reported weight which is unreliable [24]. Others use weight at the first antenatal visit which may occur after 18 weeks of gestation.

While rising levels of obesity in non-pregnant adults in developed countries are well documented, there is little information based on the accurate measurement of obesity levels in pregnancy [23]. In our own hospital, the overall obesity level is 16.6%, and nearly one in fifty is morbidly obese with a BMI $>39.9 \text{ kg/m}^2$ [29]. In an analysis from seven states in 2004–2006 using the Pregnancy Risk Assessment Monitoring System, 21.1% of women were obese and the overall prevalence of GDM was 4.0% [30]. The prevalence of GDM was 2.3% in normal women, 4.8% in overweight women, 5.5% in women with mild obesity and 11.5% in women with moderate/severe obesity. However, BMI calculations were based on self-reported prepregnancy weight. It was also unclear about what percentage of the population was screened and how.

In a meta-analysis of 20 studies published before 2006, the risk of developing GDM relative to normal women found that unadjusted ORs were 2.1 for overweight women, 3.6 for obese women and 8.6 for extremely obese women [1]. This meta-analysis, however, had limitations. Different diagnostic criteria were used for GDM and BMI categorization was also varied. The inclusion of studies with screening programs based on selective risk was a potential source of bias because obesity is a risk factor commonly used for selection. Adjusted ORs also resulted in a reduced risk of GDM with obesity which may be associated with confounding variables such as advancing age and previous obstetric history.

In a study of white European women attending our own hospital, 547 were screened selectively using the 100 g OGTT [31]. Compared with overweight women, women with mild obesity were not more likely to have an abnormal result but women with moderate to severe obesity were more likely to have an abnormal result ($P=0.008$). The risk of an abnormal OGTT result increased at the 90th centile for BMI which was 33.0 kg/m^2 and not 30.0 kg/m^2 . Nearly one in four women in this study with moderate or severe obesity had an abnormal 100 g OGTT.

In a study of women with moderate to severe obesity, 100 women were offered screening using the 100 g OGTT before 20 weeks of gestation, and if it was normal, the OGTT was repeated at 28 weeks of gestation [20]. Of the 88 who complied, 20.5% ($n=18$) had an abnormal OGTT. Of the 88, 10.8% ($n=10$) had an abnormal early OGTT and 9.8% ($n=8$) had an abnormal late OGTT. This suggests that many obese women diagnosed with GDM may have impaired glucose tolerance before pregnancy and raises questions about the optimum gestational age for screening in women who are obese. Screening should be performed early, and if negative, screening should be performed again at 24–28 weeks. This is to ensure that GDM will not be missed or the diagnosis will not be delayed. There is a lack of outcome data for treating GDM earlier in pregnancy, and early treatment outcomes may depend on early pregnancy BMI levels and/or GWG before diagnosis [3, 32].

Risks and benefits of screening for GDM

There continues to be considerable debate about the risks and benefits of screening for GDM and the optimum management once the diagnosis is made [18, 33–36]. There is a consensus that all obese women with a BMI $>29.9 \text{ kg/m}^2$ should be screened. In certain ethnic groups, the diagnosis of obesity should be made at a lower BMI [6, 31]. In women who have moderate or severe obesity, there is a strong case for screening for T2DM at the first opportunity, and if the OGTT is normal, screening again at 24–28 weeks for the onset of GDM [20].

One of the disadvantages of screening for GDM, however, is that it may lead to more testing, more ultrasound examinations and more interventions such as induction of labor and CS. Sonography evaluation of fetal growth in obese women is technically challenging and may result in the overdiagnosis of fetal macrosomia and thus an unnecessary intervention. Obese women overall

are more likely to require CS even in the absence of GDM [37]. Induction of labor in an obese woman is more likely to be unsuccessful, which increases the risk of an emergency CS. The associations between GDM and adverse clinical outcomes such as primary CS in obese women may indeed strengthen if the obstetrician is not blinded to the presence of mild maternal hyperglycemia as in the HAPO study [19]. The increase in CS rates in obese women with GDM may become a self-fulfilling prophecy that proves hazardous for all concerned as the risks of major surgery increase as obesity levels increase.

A comprehensive systematic review and meta-analysis quantified the risk of developing T2DM in women diagnosed with GDM [38]. Twenty studies involving 675,455 women were selected. Compared to women who had a normoglycemic pregnancy, women diagnosed with GDM had an increased RR for T2DM of 7.4 (95% CI 4.8–11.5). However, 98% of the women studied were from a retrospective Canadian cohort where the RR was 12.7 with a mean follow-up just over 5 years. The influence of maternal obesity on the index pregnancy was not recorded, but in two studies maternal obesity at follow-up was associated with a 10-fold increased risk of T2DM, albeit with wide confidence intervals.

In the meta-analysis, the diagnosis of GDM was not standardized, the duration of follow-up varied and sub-categorization of obesity levels was not reported. The authors concluded that GDM was a low-cost, natural screening test for T2DM. This raises the possibility that in obese women with GDM the implementation of cardio-protective interventions may pay rich dividends later in a woman's life. The ADA has recommended that women with GDM undergo testing every three years unless they were in the pre-diabetes range which would require that they undergo annual testing [8]. However, the impact of BMI categorization had not been considered.

Conclusion

Based on the implementation of the HAPO findings, the number of women diagnosed with GDM will more than double and one in three pregnancies in obese women may be complicated by GDM, which raises concerns if maternal obesity levels remain high. Despite epidemiological evidence that there is a strong relationship between maternal obesity and DM diagnosed during pregnancy, there remain considerable uncertainties about the strength of the relationship, what underpins it etiologically and what interventions before, during and after pregnancy may

lead to improved clinical outcomes subsequently for the woman and her baby and indeed future offspring.

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