Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Evidence to support the classification of hyperglycemia first detected in pregnancy to predict diabetes 6–12 weeks postpartum: A single center cohort study

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ARTICLE INFO

Article history:
Received 3 April 2020
Received in revised form
24 June 2020
Accepted 3 September 2020
Available online 10 September 2020

Keywords:
Hyperglycemia first detected in pregnancy
Overt diabetes mellitus
Gestational diabetes mellitus
Postpartum diabetes
Prevalence
Predictive factors

ABSTRACT

Aims: Diagnostic criteria for type 2 diabetes mellitus (T2DM) applied to women with gestational diabetes mellitus (GDM) may predict postpartum T2DM but requires validation.
Methods: Women with GDM aged ≥ 18-years were prospectively evaluated 6–12 weeks after delivery at Tygerberg Hospital, Cape Town, South-Africa (November 2015- December 2018). Glucose status at GDM diagnosis was categorized into i) International Association for Diabetes in Pregnancy Study Group (IADPSG) T2DM (fasting glucose ≥ 7 mmol/L and/or 2hr-glucose ≥ 11.1 mmol/L) or ii) modified National Institute for Care Excellence (NICE) GDM (fasting glucose ≥ 5.6 mmol/L-6.9 mmol/L and/or 2hr-glucose ≥ 7.8 mmol/L-11 mmol/L) and compared with postpartum OGTT.
Results: IADPSG T2DM and NICE GDM was present in 35% (n = 64) and 65% (n = 117) of the 181 women who completed the 8 ± 2 weeks postpartum evaluation respectively. Postpartum, the prevalence of T2DM and prediabetes was 26% (n = 47/181) and 15% (n = 28). Antenatal IADPSG T2DM categorization identified 31/47 women with postpartum T2DM (sensitivity 75%; specificity 48%). All of the modified NICE GDM category women who developed T2DM (n = 16/117) had elevations of both fasting and 2hr-glucose values antenatally.
Conclusion: The utility of the IADPSG T2DM criteria to predict T2DM postpartum is confirmed. Women with both fasting and 2hr-glucose values above GDM cut-offs emerged as another high-risk category.

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https://doi.org/10.1016/j.diabres.2020.108421
0168-8227/

1. Introduction

The epidemic of Type 2 Diabetes Mellitus (T2DM) is a serious public health issue with available resources insufficient to offset the anticipated complications [1–3]. However, the T2DM burden can be greatly decreased when timely diagnoses are made and appropriate interventions employed [3]. T2DM and its metabolic precursors, obesity and prediabetes, are traditionally linked to aging [4] but currently the problem also extends to younger populations. The significance of "diabesity" in younger women is revealed during pregnancy. Hyperglycemia in pregnancy affects 1 in 7 live births [5]. When the self-perpetuating nature of the T2DM cycle through metabolic imprinting of the fetus is considered, it is clear why the health of future generations is also at risk [6–9]. This risk to the offspring, together with the mother's risk to develop overt diabetes in the future makes hyperglycemia during pregnancy one of the greatest current public health concerns [5].

The unfavorable perinatal consequences associated with hyperglycemia in pregnancy were confirmed in the landmark Hyperglycemia and Adverse Perinatal Outcome (HAPO) trial [10,11]. The HAPO trial demonstrated that glucose levels previously considered normal in pregnancy do confer maternal and fetal risks, and that the degree of hyperglycemia correlates with risk [11]. Consequently, the International Association for Diabetes in Pregnancy Study Group (IADPSG) proposed stricter diagnostic criteria for gestational diabetes mellitus (GDM) [12]. The lower GDM diagnostic fasting glucose level remains controversial in low-middle-income countries [13]. This controversy centers around the logistic and financial challenges the IADPSG criteria impose on overstretched healthcare systems [13,14].

In South Africa, resource constraints limit optimal screening and management of non-communicable diseases such as T2DM.Whilst universal screening for GDM is ideal, this is seldom achieved outside of research settings. During pregnancy, the access to healthcare usually improves. Hyperglycemia is often first detected in pregnancy due to GDM screening, (usually selective and based on risk factors) performed at antenatal clinics. This diagnosis thus includes a wide spectrum of glucose abnormalities ranging from mild to overt hyperglycemia.

The IADPSG categorizes pregnant women who meet WHO diagnostic criteria for T2DM (fasting plasma glucose of $\geq$ 7 mmol/l and/or 2 h post 75 g glucose value (2hr PG) $\geq$ 11.1 mmol/L) as overt diabetes or T2DM even if the diagnosis occurs for the first time in pregnancy. The diagnosis of GDM is consequently reserved for women with milder degrees of hyperglycemia (fasting glucose $\geq$ 5.1 mmol/L and < 7 mmol/L and/or 2hr PG value $\geq$ 8.5 mmol/l and < 11. 1 mmol/l) [11].

At the time of the index study, the Western Cape Province of South-Africa, used diagnostic glucose thresholds similar to those proposed by the United Kingdom National Institute of Health and Care Excellence (NICE) guidelines [15,16]. GDM was diagnosed with a fasting glucose of $\geq$ 5.6 mmol/L and/or a 2hr postprandial value of $\geq$ 7.8 mmol/L exclusive of an upper level threshold [16]. This non-discriminating strategy pools women with glucose values in keeping with overt T2DM (FPG $\geq$ 7 mmol/L and/or 2hr post 75- gram glucose value (2hr PG) $\geq$ 11.1 mmol/L) with the GDM cohort.

In accordance with the American College of Obstetricians and Gynecologists (ACOG) and the NICE guidelines, the glucose status of all women with GDM are then re-evaluated with a 75-gram oral glucose tolerance test (OGTT) 6–12 weeks after delivery [16,17]. The postpartum evaluation is important for many reasons. It conclusively differentiates between GDM and pre-existing T2DM, as with T2DM first detected in pregnancy, abnormal glucose homeostasis is expected to still be present postpartum [16,17]. Secondly it offers the opportunity to reiterate the importance of a healthy lifestyle to prevent T2DM. Thirdly, it ensures timeous diagnosis of T2DM and prediabetes and facilitates optimal inter-pregnancy care and long-term metabolic control.

We hypothesized that a significant number of GDM women fulfil the IADPSG criteria for T2DM in pregnancy and investigated the clinical utility of the IADPSG T2DM criteria, retrospectively assigned to our GDM cohort, to identify individuals with pre-existing T2DM based on glucose status 6–12 weeks after delivery.

2. Materials and methods

This study prospectively evaluated women who had hyperglycemia first detected in pregnancy (HFDP) and attended the scheduled 6–12 weeks postpartum visit. The study spanned 38 months (01/11/2015 to 15/12/2018). Women aged 18 years or older with a diagnosis of GDM as defined by the locally modified NICE criteria in their most recent pregnancy were eligible for inclusion. Women with pre-existing diabetes (known or suspected type 1 diabetes mellitus and/or known T2DM) were excluded from study entry. The entire cohort received antenatal care and delivered at Tygerberg Hospital (TH), Cape Town, South Africa. Tygerberg Hospital is a secondary and tertiary public health facility with the largest catchment area in the Western Cape Province. At TH pregnant women are selectively screened using risk factors. Due to resource constraints, formal 75-gram OGTTs are not performed, rather, fasting and 2hr post-breakfast capillary glucose values are used. The breakfast is brought by the patient and is therefore not standardized. This approach has been carefully described elsewhere [18–20]. Women with GDM are routinely booked for a postpartum OGTT at TH, performed 6–12 weeks after delivery.

The diagnostic glucose values in the most recent pregnancy were re-categorized postpartum with either IADPSG T2DM or NICE GDM based on NICE criteria and upper level IADPSG cut-offs (modified NICE GDM). Women were thus retrospectively re-categorized as overt IADPSG T2DM if antenatal glucose values exceeded WHO diagnostic thresholds.

Antenatal data was collected at the postpartum visit and verified with electronic hospital patient records. Anthropometric (height, weight) measurements and documentation

of glucose control during pregnancy was sourced from electronic hospital and clinic records. Glucose measurements were verified with the National Health Laboratory Service (NHLS). Antenatal use of prescribed medicine was self-reported.

Pharmacological therapy for hyperglycemia in GDM women with HFDP following delivery is routinely discontinued, provided that they do not require insulin postpartum and that the glucose profiles prior to discharge remains normal.

Clinical data was collected at the postpartum visit on standardized data sheets and included demographic parameters (breastfeeding, parity, education, employment status and family history) and a list of current medication. A dedicated diabetes nursing sister performed all anthropometric and blood pressure measurements, blood sampling and the OGTT according to standardized protocols. Women were excluded if they were not fasted for the OGTT or if they continued use of hypoglycemic medication.

Postpartum glucose homeostasis was evaluated with a 75-gram OGTT. The participants ingested the pre-measured glucose for the postpartum OGTT within 10-minutes and venous samples for HbA1c, fasting plasma glucose (FPG) as well as 2hr post glucose load plasma glucose (2hr-PG) were obtained. Women in whom a glucose test result was only available at one of the OGTT time-points, were classified on the single value.

Biochemical measurements were performed at the NHLS, a South African National Accreditation Service accredited laboratory. Plasma glucose was collected in sodium fluoride tubes and was measured by means of the glucose oxidase method on the Siemens ADVIA 1800 platform from 1 Nov 2015 to 12 September 2016. The assay has a measuring range from 0 to 41.6 mmol/L with a reported coefficient of variation (CV) of 1.7% at a glucose level of 4.4 mmol/L and 17.5 mmol/L respectively. From 13 September 2016 the glucose was measured by means of the hexokinase method on the Roche Cobas 6000 platform (Roche Diagnostics, Mannheim, Germany) platform. The assay has a measurement range from 0.11 to 41.6 mmol/L with a reported CV of 1.3% at a glucose level of 5.38 mmol/L and 1.1% at 13.4 mmol/L. HbA1c was determined. HbA1c was initially measured by a Siemens Advia 1800 (Siemens Diagnostics, New York, United States) initially and changed over to the Roche Cobas c501 (Roche Diagnostics, Mannheim, Germany) on 12 September 2016. The methodology used in the Roche is turbidimetric inhibition immunoassay, in comparison to Siemens Advia utilizing latex agglutination inhibition. The measuring range of the Roche platform is 4.2% – 20.1% (22 to 195 mmol/mol and more) with a CV of 1.3% at HbA1c of 5.3% (34 mmol/mol) and 1.1% at HbA1c of 9.9% (85 mmol/mol). The measuring range of the Siemens is 0.23% – 17.8% (<9 to 171 mmol/mol) with a coefficient of variation of 0.8% at HbA1c of 5.08% (32 mmol/mol) and 1.3% at HbA1c of 10.1% (87 mmol/mol).

Statistical analysis was performed by using IBM SPSS Statistics version (25). Numbers are reported as n (%). Continuous variables are reported as mean ± SD or 95% confidence intervals (CI's). A two-sided $P < 0.05$ was considered statistically significant. Categorical risk factors were cross-tabulated as well as continuous variables, Chi-squared and t-tests were performed respectively (if there was a normal distribution).

The Stellenbosch University Health Research Ethics approved the study HEA-2019–8297. A waiver of informed consent was granted as de-identified antenatal data was obtained retrospectively and because the study protocol forms part of the standard of care at the TH postpartum clinic.

3. Results

The study population consisted of 181 participants. Treatment with medical nutritional therapy (MNT) ensured glucose targets in only 27/181 (15%) of women with GDM. Most of the women required a combination of MNT and metformin to achieve optimal glucose control (129/181, 71%). A small number of women required insulin therapy in addition to MNT and metformin (25/181, 14%). Metformin was well tolerated in most, with gastrointestinal side-effects necessitating withdrawal in only two participants.

Complete antenatal and postnatal glucose evaluation profiles (paired fasting and 2hr glucose levels) were available in 91% (n = 165/181) and 85% (n = 154/181) of participants respectively. The 2hr glucose value were unavailable in 16 women for the antenatal and in 23 women for the postnatal evaluation, whereas the fasting glucose assessment was not documented in only 4 of the participants tested postpartum.

3.1. *Re-categorization of antenatal glucose status*

In pregnancy, all women had GDM as defined by the NICE criteria. For the purpose of the study, they were re-categorized based on IADPSG criteria for overt diabetes in pregnancy as either IADPSG T2DM or as modified NICE GDM (Fig. 1). Patients with IADPSG T2DM fulfilled WHO criteria for overt diabetes at GDM diagnosis. Individuals re-categorized as modified NICE GDM had the WHO diagnostic criteria added as an upper limit i.e. the two categories were mutually exclusive.

An elevated fasting glucose was documented in 133/181 women at GDM diagnosis, representing 73% of the study population. Upon re-categorization most of the elevated fasting glucose values (77/133; 57%) remained in the NICE GDM range (glucose $\geq$ 5.6 mmol/L and < 7 mmol/L) with 56/133 values meeting criteria for IADPSG T2DM.

The glucose at the 2hr time-point was elevated in the majority (129/165; 78%) of women in whom 2hr values were available (16 missing values at this time point). Most 2hr values (n = 100/129; 78%) were in the NICE GDM range (glucose $\geq$ 7.8 and < 11.1 mmol/L) upon re-categorization. The balance of 29/129 (22%) elevated 2 h-glucose values exceeded the overt diabetes threshold (>11.1 mmol/L).

Just over a third (n = 64/181; 35%) of women fulfilled IADPSG criteria for overt T2DM at GDM diagnosis. Overt T2DM was based on either a fasting value or a 2hr value or both values in keeping with WHO diagnostic criteria (Fig. 1). The antenatal re-categorization to T2DM was based on an elevated fasting glucose value of $\geq$ 7 mmol/L in 35/64 women, on a 2hr glucose level $\geq$ 11.1 mmol/L in 8/64 women and on concurrent elevated fasting and 2hr values in 21 women. In

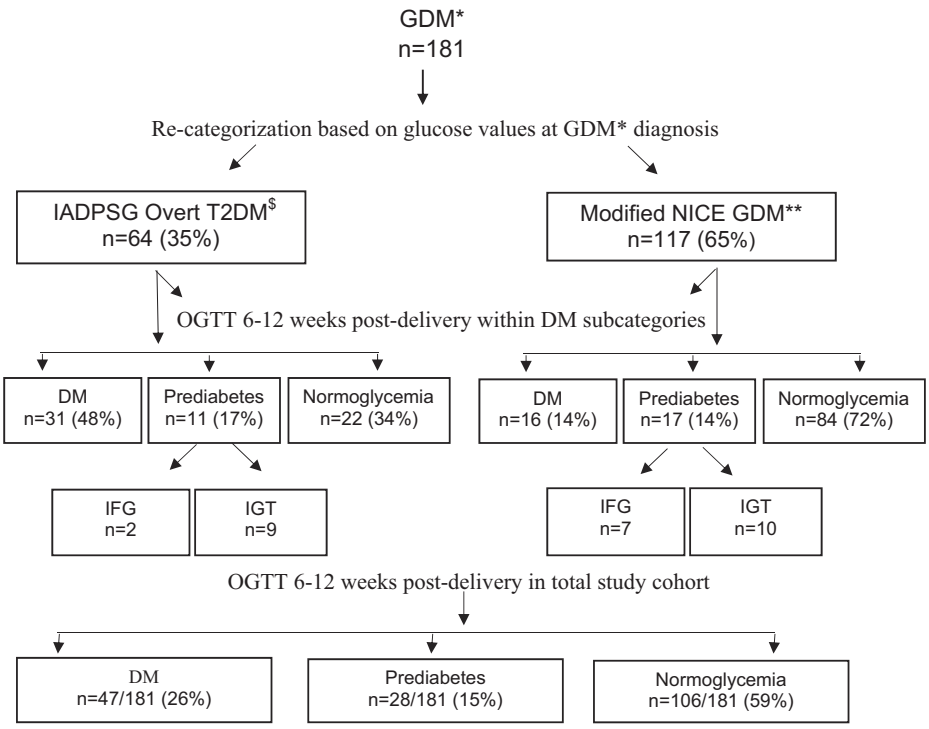

Fig. 1 – Recategorization of antenatal and categorization of postpartum glucose status. *GDM = Gestational diabetes mellitus based on National Institute of Care excellence (NICE) criteria (fasting glucose ≥ 5.6 mmol/L and/or 2hr postprandial ≥ 7.8 mmol/L). $Overt IADPSG T2DM = Fasting glucose > 7 mmol/L and/or 2 h glucose > 11.1 mmol at GDM diagnosis. **GDM based on fasting glucose ≥ 5.6 mmol/L and < 7 mmol/L and/or 2hr postprandial load ≥ 7.8 mmol/L and < 11.1 mmol/L. DM = Diabetes Mellitus.

women re-categorized as T2DM, 56/64 (88%) women thus had a fasting value of ≥ 7 mmol/L with or without an elevated 2hr glucose measurement.

An elevated glucose value at both time points (fasting glucose value ≥ 5.6 mmol/L and a concurrent 2hr value ≥ 7.8 mmol/L) was documented in 88(49%) of the 181 women. Criteria in keeping with IADPSG T2DM in this subset was present in 52 women (fasting value ≥ 7 mmol/L only in 23 women, a 2hr value exceeding 11.1 mmol/L only in 12 women and T2DM criteria at both time points in 17 participants). In these women who exceeded GDM thresholds at fasting and at 2hrs, 59% were thus re-categorized as IADPSG T2DM.

3.2. *Descriptive characteristics of the different study cohorts*

Descriptive characteristics of the total study cohort, the re-categorized modified NICE GDM group and the re-categorized IADPSG overt T2DM group are summarized in Table 1. The mean age of study participants was 32 ± 5 years, the majority were multigravidas (155/181; 86%) and the mean gestation at antenatal diagnosis 23.5 ± 8.8 wee ks. The mean gestation at delivery was 37 ± 4 weeks with caesarean sections performed on 46% of the total cohort (84/181). At diagnosis, an HbA1c ≥ 6.5% in keeping with T2DM was present in 40% of women. There were 9 third trimester losses, with 4 of the losses in women who met IADPSG criteria for T2DM. Twenty percent of babies born to these mothers were macrosomic (birth weight > 4000 g). Modified NICE GDM women tended to be younger, more booked after 24 weeks and they were diagnosed with hyperglycemia at a later gestation compared to the women re-categorized as T2DM. Women with T2DM had a first degree relative with diabetes in near 90% of cases (56/64) compared to a lower percentage reported in the modified NICE GDM group (35%).The vast majority of women in both groups had BMI measurements in the WHO obese category (≥30 kg/m^2), and mean weight did not differ significantly between the two cohorts.

3.3. *Postpartum outcome in re-categorized diabetes subgroups*

The mean interval from delivery to postpartum evaluation was 8 ± 2 weeks. Breastfeeding status was available in most (177/181) women at the time, with exclusive breastfeeding reported by 139 mothers. The BMI at antenatal booking did not differ significantly between the diabetes sub-groups (Table 1, p = 0.21). Repeat anthropometry performed at the postpartum visit was also similar between the two diabetes subgroups. A trend towards a lower BMI in the IADPSG T2DM was observed, but did not reach statistical significance (p = 0.08).

Glucose homeostasis remained abnormal in 41% (75/181) of the study cohort 6–12 weeks after delivery. Glucose values in keeping with T2DM and prediabetes respectively were present in 47/75 and 28/75 of these women (Fig. 1).

The postpartum biochemical assessments are tabulated in Table 2. An elevated fasting blood glucose was present in

Table 1 – Descriptive characteristics of study participants.

Descriptive characteristics	Total Study cohort (n = 181)	GDM (NICE modified) (n = 117)	T2DM (IADPSG) (n = 64)	P value
Age (years)	32(5)	31(5)	33(6)	0.025
Advanced maternal age > 40 years	16(9%)	7(6%)	9(14%)	0.101
Level of education				
Primary only	20(11%)	12(10%)	8(13%)	0.623
Secondary	135 (75%)	92(79%)	43(67%)	0.293
HIV positive status	15(8%)	8 (7%)	7(11%)	0.647
First degree relative with T2DM	97(51%)	41 (35%)	56 (88%)	0.049
Gravidity	3(2)	3(2)	3(2)	0.397
Primigravida	26 (14%)	15 (13%)	11(17%)	0.511
Parity	2(1)	2(1)	2(1)	0.913
Gestation				
Booking (weeks)	13.8(5.9)	14.1(6.0)	13.4(5.7)	0.401
Booking after 24 weeks	112(59%)	81(69%)	31(48%)	0.005
Antenatal GDM diagnosis (weeks)	23.5(8.8)	25.5(7.8)	20.2(9.4)	<0.0001
Anthropometry at booking visit				
Weight in kg	94(22)	96(23)	90(19)	0.072
BMI in kg/m^2	37(9)	38(10)	36(7)	0.205
BMI > 30 kg/m^2	163(86%)	91(78%)	61(95%)	0.920
Biochemistry at diagnosis				
Fasting glucose mmol/L	6.6(1.8)	5.6(0.8)	8.2(1.8)	<0.0001
2hr glucose mmol/L	9.1(2.5)	8.1(1.6)	11.2(2.9)	<0.0001
HbA1c % (mmol/mol)	6.6(1.6)	6.2(1.3)	7.3(1.6)	<0.0001
HbA1c $\geq$ 6.5%	74(40%)	28(24%)	46(72%)	<0.0001
Hemoglobin < 10 g/dl	8 (4%)	6(5%)	2(1%)	0.575
Birthweight in grams	3318(846)	3352(762)	3257(938)	0.470
Macrosomia > 4000 g	38 (20%)	25(21%)	13(20%)	0.852
Third trimester loss	9(5%)	5(4%)	4(6%)	0.298

Values are given in mean and SD or number (%) unless otherwise specified. NICE GDM = National Institute of Health Care Excellence cut-off for diagnosing Gestational Diabetes Mellitus excluding Overt Diabetes (fasting glucose $\geq$ 5.6 mmol/L to < 7 mmol/L and 2 h-hour glucose $\geq$ 7.8 mmol/L to 11.1 mmol/L). IADPSG T2DM = International Association for Diabetes in Pregnancy Study Group criteria for Overt Diabetes (fasting plasma glucose of $\geq$ 7 mmol/l and/or 2 h post 75 g glucose value (2hr PG) $\geq$ 11.1 mmol/l).
BMI = Body Mass Index in kg/m^2 ;p-values refer to comparison between NICE GDM and IADPSG T2DM cohorts.

Table 2 – Postpartum biochemical assessment of glucose homeostasis.

Biochemical parameter	Total cohort (n = 181)	*Postpartum glucose categories* Normal (n = 106; 59%)	Prediabetes (n = 28; 15%)	Diabetes (n = 47; 26%)
Elevated FPG	45(25%)		9/28*(32%)	36/47**(77%)
Elevated 2hr PG	47(26%)		19/28* (68%)	28/47**(60%)
Mean fasting glucose in mmol/L	6.1 ± 2.5	4.8 ± 0.5	5.7 ± 0.9	9.3 ± 3.2
Mean 2hr glucose in mmol/l	7.5 ± 3.3	5.5 ± 1.1	8.2 ± 1.5	13.0 ± 3.1
HbA1C				
%	6.1 ± 1.2	5.5 ± 0.6	6.0 ± 0.6	7.5 ± 1.5
Mmol/mol	41 ± 1.2	37 ± 0.6	42 ± 0.6	58 ± 1.5
Number of participants with concurrent HbA1c's	172	100	27	45
HbA1c diagnostic of diabetes ($\geq$6.5%)	40/172(23%)	6/100(6%)	3/27(11%)	36/45(76%)
HbA1c indicative of prediabetes ($\geq$5.7% – 6.4%)	48(28%)	22/100(22%)	18/27(37%)	8/45(18%)

Values are given in mean and SD or number (%) FPG = Fasting plasma glucose. 2hr PG = . Plasma glucose 2hrs after 75-gram OGTT. Value exceed WHO cut off level for *pre-diabetes and **diabetes.

most women with T2DM (36/47; 77%), both fasting and 2hr values were diagnostic for T2DM in 17 women. A diagnosis of T2DM was made based on an elevated fasting value only in 19/47 (40%) and on an elevated 2hr value only in 11/47 (23%) of women. The diagnosis of prediabetes was based on impaired fasting glucose (IFG) in 9/28 (32%) and on impaired glucose tolerance (IGT) in 19/28 (68%) women.

Near half (31/64) of the women with antenatal re-categorized IADPSG T2DM had persistent T2DM postpartum and 11 women had glucose values in keeping with

prediabetes. Twenty-two women within this subgroup reverted to normal glucose homeostasis postpartum (34%). The majority of these women indicated exclusive breastfeeding up to the time of evaluation (14/22; 64%).

In the modified NICE GDM group, the majority of women had normal glucose homeostasis at postpartum assessment (84/117; 72%). A diagnosis of T2DM was confirmed in 16 women (14%) within this diabetes subcategory (Fig. 1).

The sensitivity, specificity, positive predictive value and negative predictive value of the antenatal IADPSG T2DM criteria to predict persistently abnormal glucose homeostasis and T2DM at 6–12 weeks postpartum are tabulated in Table 3. The antenatal IADPSG T2DM criteria demonstrates a sensitivity of 69% and 75% to predict abnormal glucose homeostasis respectively at early postpartum assessment.

4. Discussion

In the study of women with hyperglycemia first detected in pregnancy (HFDP), one out of every three women retrospectively fulfilled IADPSG criteria for T2DM.

In the women retrospectively assigned an antenatal diagnosis of IADPSG T2DM, abnormal glucose homeostasis was documented in two-thirds (42/65) at early postpartum assessment with diagnostic criteria for overt T2DM present in 48% (31/64). The majority of women with postpartum T2DM had antenatal IADPSG T2DM (31/47; 66%). All 16 women with GDM based on the modified NICE criteria who had sustained T2DM postpartum, met glucose criteria for GDM at both time-points measured i.e. at fasting and at 2hrs.

In the local cohort, women at highest risk for sustained T2DM at early postpartum follow-up are both those with antenatal IADPSG T2DM and those with modified NICE GDM where both glucose values exceed diagnostic thresholds.

The latter half of normal pregnancy is a state of increased insulin resistance (IR) aimed at generating a glucose gradient towards the fetus. In women with adequate pancreatic reserve, insulin secretion increases accordingly. In GDM, mild hyperglycemia develops due to an insufficient increase in insulin secretion to respond appropriately to the physiological state of IR, therefore unmasking chronic maternal β-cell defect. Upon delivery, insulin sensitivity returns to pre-pregnancy levels within hours [21].

Women re-categorized as having GDM based on modified NICE criteria represent women with a milder degree of hyperglycemia. Glucose homeostasis is expected to normalize in these women soon after delivery. This was indeed the case in the majority of these women with documented normal glucose values early postpartum in 84/117 women with GDM (72%). All women with modified NICE GDM who progressed to T2DM postpartum had increased glucose values at both measured time-points at GDM diagnosis (paired fasting and 2hr). So the inability to maintain both fasting and postprandial glucose values may represent a GDM subgroup at higher risk of postpartum T2DM. GDM populations are indeed heterogeneous with β-cell dysfunction and IR contributing to hyperglycemia to varying degrees. Liu et al defined the heterogeneity of GDM by categorizing GDM women into those with predominant β-cell dysfunction, predominant IR, or those with both beta cell dysfunction and IR (mixed group). He noted that the mixed group represent the group with the highest risk for adverse perinatal outcomes [22]. Benhalmina et al also demonstrated differences in perinatal outcome between women with predominantly IR versus those with predominant β-cell dysfunction but failed to show any difference in maternal glucose homeostasis between these two groups 14 weeks after delivery [23]. The magnitude of hyperglycemia and the presence of postpartum T2DM were significantly less in the aforementioned studies compared to findings in our study.

The 43% prevalence of postpartum hyperglycemia following HFDP in the current study is concerning but has been reported before in a similar population [2]. This suggests pre-existing β-cell dysfunction and abnormal glucose homeostasis prior to the index pregnancy. The limited screening for T2DM outside of pregnancy, the local selective screening protocol in pregnancy and the adoption of the modified NICE guidelines for GDM diagnosis with no upper glucose threshold for T2DM all potentially contribute.

The prevalence of sustained T2DM in our cohort as early as 6–12 weeks postpartum is very close to the 45% reported by Chivese et al after 5–6 years follow-up in a similar cohort from Cape Town [24]. This finding implies more advanced disease in our cohort who had sustained T2DM as early as 6 weeks postpartum in a significant percentage of women with HFDP. The authors previously reported a 46% prevalence of abnormal postpartum glucose homeostasis early postpartum (DM in 27%) in a smaller cohort of patients (n = 78) [2]. Univariate analysis in the mentioned study identified the degree of hyperglycemia at diagnosis as a significant risk factor for early postpartum diabetes [2,25].

In a recent study conducted in an urbanized adult community within the TH reference area, the crude prevalence of T2DM was 28.2% (age-adjusted 26.3%, 95% confidence interval (CI) 22.0 – 30.3), with undiagnosed T2DM present in 18.1% (age-adjusted 16.8%, 95% CI 13.3 – 20.4) of the study population. This study indicated an enormous increase in T2D prevalence based on the percentage of previously undiagnosed individuals. Interestingly, almost half of the study population were women younger than 49 years. The respective

Table 3 – The utility of IADPSG T2DM criteria to predict abnormal glucose 6–12 weeks after GDM.

Prediction	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
T2DM	75%	48%	59%	65%	61%
Abnormal glucose[$]	69%	79%	77%	72%	74%

* IADPSG T2DM includes either antenatal fasting glucose value > 7 mmol/L and/or 2 h post glucose load > 11.1 mmol/L [$] Abnormal glucose homeostasis = T2DM and prediabetes.

crude prevalence of T2D was 7.7% and 14.7% in the age groups 30–39 years and 40–49 years [26]. Pregnancy is often the first exposure to formal health care in resource-limited settings. The high prevalence of sustained T2DM following HFDP may reveal the prevalence of undiagnosed T2DM in the background population of women in the reproductive age category and support the need to distinguish between GDM and T2DM in HFDP. Antenatal differentiation further permits timely identification of a notable subgroup of women with T2DM first identified when presenting with HFDP.

Although the distinction between IADPSG T2DM and NICE GDM do not necessarily directly influence the antenatal management of hyperglycemia, it fosters added awareness and alertness of persistent hyperglycemia postpartum. Long-term follow-up after GDM is suboptimal globally despite extensive efforts to engage women [27]. Identification of women at highest risk for sustained hyperglycemia should be prioritized considering the undisputable benefits of early intervention [27,28].

We report that IADPSG T2DM in pregnancy pose a significant risk of sustained T2DM postpartum, however it was not a universal finding. Twenty-two women within this subgroup reverted to normal glucose homeostasis and eleven improved to a state of pre-diabetes. All women had HFDP with no prior knowledge or guidance as to ideal nutrition. Whilst the improved glucose homeostasis postpartum may denote improved insulin sensitivity after delivery, medical nutrition education coupled with the application of feasible dietary modifications likely also first ensued in the index pregnancy.

Another maternal protector to consider is breastfeeding. Fourteen of the 22 women who reverted to normal glucose homeostasis reported exclusive breastfeeding at the time of the postpartum visit. A systematic review of published studies suggests that women with GDM are less likely to exclusively breastfeed their babies and tend to breastfeed for a shorter time compared to women without GDM [29].

Breastfeeding has been reported to have both short- and long-term benefits on glucose metabolism in GDM women. Long-term benefits include a decreased risk of developing T2DM. Similarly, breastfeeding has been shown to have favourable short-term effects within cross-sectional and prospective study designs. Documented short-term effects of breastfeeding include a lowering of total area under the curve for postpartum glucose, and lower mean fasting and 2-hr glucose levels 4–12 weeks postpartum [30]. Moreover, improved glucose levels are attributed to enhanced pancreatic β-cell function demonstrated by lowered insulin disposition indices as early as 3 months postpartum [31]. In the Atlantic Diabetes in Pregnancy study, the presence of persistent hyperglycemia following OGTT was decreased by 10% in breastfeeding women compared to women who formula-fed 12 weeks postpartum [32]. While this may signify improved pancreatic function, the impact of breastfeeding on glucose handling at the time of the OGTT have also been studied. Gunderson et al. found a small but significant reduction in the 2-hr glucose values (−5%), but no effect on fasting glucose and insulin levels [33]. Our study did not specifically exclude breastfeeding at the time of the OGTT and it is thus conceivable that most women who breastfed continued to do so during the performance of the OGTT. The magnitude of the change Gunderson observed in the 2-hr glucose values, however, makes it unlikely that the impact on our postpartum assessment and glucose categorization was significant.

Limitations of our study involve an inability to report on the underlying physiological processes leading to hyperglycemia in pregnancy. Such assessment may be valuable for future risk stratification and management. The retrospective re-categorization of antenatal glucose status did not include a subgroup with IADPSG GDM (utilising lower fasting glucose thresholds than NICE). This could have provided information on an even milder spectrum of hyperglycemia in pregnancy. Formal antenatal 75 g OGTTs were not performed. The 6–12 weeks post-partum timeline is early for evaluation of the development of de novo T2DM and it is plausible that the sensitivity and specificity of IADPSG T2DM criteria to identify development of T2DM will increase with longitudinal follow-up. We did not perform a statistical sample size calculation for this non-intervention study, but the number of 181 women adequately addressed the study objectives.

5. Conclusion

In this study a third of women with hyperglycemia first detected in pregnancy (HFDP) retrospectively fulfilled IADPSG criteria for T2DM. IADPSG T2DM predicted sustained DM early postpartum with a sensitivity of 75%. Women with antenatal IADPSG T2DM and women with modified NICE GDM in whom glucose values exceeded the diagnostic thresholds both at fasting and after a glucose load were at highest risk for T2DM at early postpartum follow-up. Universal screening and lower diagnostic cut-offs for GDM may not be possible in resource constrained health care systems, but IADPSG T2DM criteria and concordantly elevated glucose values in women with GDM indicate high risk for postpartum glucose abnormalities and are noteworthy.

REFERENCES

[1] Dagenais GR, Gerstein HC, Zhang X, McQueen M, Lear S, Lopez-Jaramillo P, Mohan V, Mony P, Gupta R, Kutty VR, Kumar R. Variations in diabetes prevalence in low-, middle-, and high-income countries: Results from the prospective urban and rural epidemiology study. Diabetes care. 2016 Mar 10:dc152338.

[2] Coetzee A, Mason D, Hall DR, Conradie M. Prevalence and predictive factors of early postpartum diabetes among women with gestational diabetes in a single-center cohort. Int J Gynecology Obstetrics 2018.

[3] Sortsø C, Komkova A, Sandbæk A, Griffin SJ, Emneus M, Lauritzen T, et al. Effect of screening for type 2 diabetes on healthcare costs: a register-based study among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. Diabetologia 2018;61(6):1306–14.

[4] Hillier TA, Pedula KL. Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. Diabetes Care 2001;24(9):1522–7.

[5] International Diabetes Federation IDF Diabetes Atlas 7th Edition. http://www.diabetesatlas.org/ Accessed 2018; July 18.

[6] Dabelea D, Crume T. Maternal environment and the transgenerational cycle of obesity and diabetes. Diabetes 2011;60(7):1849–55.
[7] Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, Damm P. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes Care 2008;31(2):340–6. https://doi.org/10.2337/dc07-1596.
[8] Wicklow Brandy A, Sellers Elizabeth AC, Sharma Atul K, Kroeker Kristine, Nickel Nathan C, Philips-Beck Wanda, Shen Garry X. Association of gestational diabetes and type 2 diabetes exposure in utero with the development of type 2 diabetes in first nations and non–first nations offspring. JAMA Pediatr 2018;172(8):724. https://doi.org/10.1001/jamapediatrics.2018.1201.
[9] Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Maternal-Fetal Medicine 2000;9(1):83–8.
[10] Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, et al. Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care 2012;35(3):574–80.
[11] Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria: the hyperglycemia and adverse pregnancy outcome (HAPO) study. Diabetes Care 2012;35(3):526–8.
[12] International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care. 2010 Mar 1;33(3):676-82.
[13] Bhavadharini B, Uma R, Saravanan P, Mohan V. Screening and diagnosis of gestational diabetes mellitus–relevance to low and middle-income countries. Clinical Diabetes Endocrinology 2016;2(1):13.
[14] Seshiah V, Shah SN, Balaji V, Anjalakshi C, Jain R. When are we going to settle the diagnostic criteria of gestational diabetes mellitus?. J Assoc Physicians India 2019;67:70.
[15] Maternal Guideline Reference Group and the Subcommittee of the Society for Maternal and Foetal Medicine in South Africa. Diabetes in pregnancy, provincial guideline of the Western Cape, for the management of diabetes and its complications from pre-conception to the postnatal period. Western Cape: Provincial Government; 2010. https://www.scribd.com/document/.../Diabetes-in-Pregnancy-Western-Cape-Guidelines [accessed 19 July 2018].
[16] National Institute for Health and Care Excellence. Diabetes in pregnancy: Management from preconception to the postnatal period. NICE Guidelines. 2015. https://www.nice.org.uk/guidance/ng3 (accessed 15 June 2018).
[17] Smirnakis KV, Chasan-Taber L, Wolf M, Markenson G, Ecker JL, Thadhani R. Postpartum diabetes screening in women with a history of gestational diabetes. Obstet Gynecol 2005;106(6):1297–303.
[18] Hall D, du Toit MA, Mason D, Conradie M. Diabetes in pregnancy, still changing. Journal of Endocrinology, Metabolism and Diabetes of South Africa 2015;1(1):1-7. http://dx.doi.org/10.1080/16089677.2015.1069015.
[19] Marais C, van Wyk L, Conradie M, Hall D. Screening for gestational diabetes- examining a breakfast meal test. South African J Clin Nutrition 2016;29(03).
[20] Marais C, Hall D, van Wyk L, Conradie M. Randomised, cross-over trial comparing the diagnosis of gestational diabetes by oral glucose tolerance test and a designed breakfast glucose profile. Int J Gynecol Obstet 2018;141:85–90. https://doi.org/10.1002/ijgo.12427.
[21] Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci 2018;19(11):3342.
[22] Liu Y, Hou W, Meng X, Zhao W, Pan J, Tang J, et al. Heterogeneity of insulin resistance and beta cell dysfunction in gestational diabetes mellitus: a prospective cohort study of perinatal outcomes. J Trans Med 2018;16(1):289.
[23] Benhalima K, Leuridan L, Calewaert P, Devlieger R, Verhaeghe J, Mathieu C. Glucose intolerance after a recent history of gestational diabetes. Int J Endocrinol 2014;2014.
[24] Chivese T, Norris SA, Levitt NS. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLoS Med 2019;16(9) e1002865.
[25] Coetzee A, Mason D, Hall DR, Hoffmann M, Conradie M. Evidence for the utility of antenatal HbA1c to predict early postpartum diabetes after gestational diabetes in South Africa. Diabetes Res Clin Pract 2018;1(143):50–5.
[26] Erasmus RT, Soita DJ, Hassan MS, Blanco-Blanco E, Vergotine Z, Kengne AP, et al. High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: baseline data of a study in Bellville. Cape Town. South African Medical J 2012;102(11):841–4.
[27] Stuebe A, Ecker J, Bates DW, Zera C, Bentley-Lewis R, Seely E. Barriers to follow-up for women with a history of gestational diabetes. Am J Perinatol 2010;27(09):705–10.
[28] Cheung N, Byth K. Population health significance of gestational diabetes. Diabetes Care 2003;26:2005–9.
[29] Nguyen PT, Pham NM, Chu KT, Van Duong D, Van Do D. Gestational diabetes and breastfeeding outcomes: a systematic review. Asia Pacific J Public Health 2019;31(3):183–98.
[30] Kjos SL, Henry OL, Lee RM, Buchanan TA, Mishell JD. The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. Obstet Gynecol 1993;82(3):451–5.
[31] McManus RM, Cunningham I, Watson A, Harker L, Finegood DT. Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. Metabolism-Clinical and Experimental. 2001;50(6):715–9.
[32] O'Reilly M, Avalos G, Dennedy MC, O'Sullivan EP, Dunne FP. Breast-feeding is associated with reduced postpartum maternal glucose intolerance after gestational diabetes. Ir Med J 2012;105(5 Suppl):31–6.
[33] Gunderson EP, Crites Y, Chiang V, Walton D, Azevedo RA, Fox G, et al. Influence of breastfeeding during the postpartum oral glucose tolerance test on plasma glucose and insulin. Obstet Gynecol 2012;120(1):136.