Glucose intolerance in early postpartum in women with gestational diabetes : who is at increased risk?

Glucose intolerance in early postpartum in women with gestational diabetes: Who is at increased risk?

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Summary

Women with a history of gestational diabetes (GDM) have an increased risk for developing type 2 diabetes in the years after the index pregnancy. Some women with GDM already develop glucose intolerance in early postpartum. The best screening strategy for glucose intolerance in early postpartum among women with a history of GDM is still debated. We review the most important risk factors of women with GDM to develop glucose intolerance within one year postpartum. We also discuss the current recommendations for screening in early postpartum and the many challenges to organize postpartum follow up in primary care.

Introduction

Gestational diabetes (GDM) was historically defined as 'any degree of glucose intolerance with onset or first recognition during pregnancy' [1]. During pregnancy insulin resistance progressively increases and by the third trimester this can reach the degree of resistance seen in non-pregnant women with type 2 diabetes mellitus (T2DM). It has long been thought that the insulin resistance provided a short-term challenge to the β-cells, with GDM arising in those women whose β-cells were unable to meet this challenge. Progressively more data show now that the defect in β-cell compensation that characterizes GDM is chronic and probably not just acquired during pregnancy. Shortly after delivery the insulin resistance is generally restored to the pre-pregnancy level but often the chronic β-cell dysfunction persists [2, 3]. Women with a previous history of GDM are therefore at increased risk to develop T2DM [4]. Some women with GDM already develop glucose intolerance within the first year postpartum. Primary care has a crucial role in diagnosing GDM and even more in detecting progression to T2DM postpartum and counseling these women in lifestyle changes that can alter progression towards disease [5]. We review here the most important risk factors of women with GDM to develop glucose intolerance within one year postpartum and discuss the current recommendations for postpartum screening and the challenges for primary care to organize the follow up postpartum.

Screening for glucose intolerance postpartum

The American Diabetes Association (ADA) and the Endocrine Society recommendations advise screening for T2DM in all women who have had GDM at 6-12 weeks postpartum with a 2-h 75g oral glucose tolerance test (OGTT) with non-pregnancy diagnostic criteria [1,6]. A HbA1c or fasting plasma glucose (FPG) are more commonly used screening tests for diabetes in the general population. These tests are easier to perform and cheaper than an OGTT. Moreover, a reasonable sensitivity for the diagnosis of T2DM has been shown when used in the general population. Studies evaluating the use of FPG alone or FPG in combination with HbA1c in women with a recent history of GDM show conflicting results with sensitivity rates of resp. 60%-83% and 83%-90% compared to the use of an OGTT [7-9]. The measurement of HbA1c alone does not seem to perform properly in this setting as shown by a low sensitivity of 22%-65% compared to the use of an OGTT [8,10]. Beyond the first year postpartum, the ADA recommends that women with a history of GDM should have lifelong screening for the

development of glucose intolerance, at least every 3 years [1]. Currently there is insufficient evidence to recommend one test over the other and therefore HbA1c, FPG, or 2-h 75g OGTT can be used to test for diabetes.

The prevalence and risk factors of glucose intolerance postpartum also depend on the type of screening strategy and diagnostic criteria for GDM that was used. The initial criteria for diagnosis of GDM were established more than 40 years ago and were chosen to identify women at high risk for development of diabetes after pregnancy [11]. In the meantime, progressively more data emerged showing that the risk of adverse perinatal outcomes was also associated with milder degrees of hyperglycaemia during pregnancy [12]. Following these data, The International Association of Diabetes and Pregnancy Study Groups' (IADPSG) recommends now the use of a one-step diagnostic approach with an OGTT with the use of more stringent diagnostic criteria for GDM [13]. These new recommendations lead to an important increase in the prevalence of GDM but a lower proportion of these newly defined GDM women will probably progress to T2DM postpartum. When the old criteria are used, the risk of women with GDM to develop T2DM within 10 years after the index pregnancy is generally high at around 30-50% [4]. The first follow up results with the IADSPG criteria for GDM suggest lower rates, with 28.4% of women with GDM developing glucose intolerance or diabetes 1-5 years after the index pregnancy [14].

The prevalence of obesity and T2DM is increasing worldwide and also in women of childbearing age, leading to more pregnant women with undiagnosed T2DM [15]. A large proportion of "early" T2DM after GDM probably represents undiagnosed T2DM that already existed prior to conception, but that was only detected at the time of GDM screening. The goal of early postpartum testing is therefore not only to detect T2DM that has rapidly progressed after GDM but also to detect T2DM that was already present before pregnancy. The timely diagnosis and treatment of pre-existing diabetes early in pregnancy is important as these women are at an increased risk for congenital anomalies due to their greater degree of hyperglycaemia earlier in pregnancy. Many associations such as the ADA, the IADPSG and the World Health Organization recommend therefore now to screen for unknown diabetes at the first prenatal visit [1, 13,16]. This should lead to a more timely diagnosis of T2DM before or during pregnancy and will reduce the number of women with a diagnosis of persistent T2DM in early postpartum.

Risk factors for developing glucose intolerance in early postpartum

To optimize the postpartum surveillance strategy it would be useful to identify clear risk factors for early progression to glucose intolerance after GDM, so that a more personalized (and presumably cheaper) surveillance strategy could be developed adapted to the individual risk. Frequently reported clinical risk factors are maternal age, ethnicity, parity, family history of T2DM, pre-pregnancy weight, weight gain during pregnancy, a previous history of GDM, early diagnosis of GDM and requirement of insulin during pregnancy. Frequently reported biochemical risk factors are a 50g glucose challenge test (GCT) > 11.1 mmol/L and a high FPG on the diagnostic OGTT during pregnancy. After adjustment for confounders often only a few of these risk factors remain statistically significant and the FPG value on the diagnostic OGTT during pregnancy seems to be the most powerful predictor [17]. Breastfeeding is generally considered to have a protective effect on the risk to develop glucose intolerance postpartum. A recent study has shown that the prevalence of persistent hyperglycaemia was significantly lower in women who breast-fed versus bottle-fed 12 weeks postpartum (8.2% versus 18.4%) [18].

Since our aim was to specifically evaluate risk factors to develop glucose intolerance early after the delivery in women with GDM, we restricted our literature search to articles specifically analyzing risk factors for the development of glucose intolerance during the first year postpartum. By an electronic search of Medline from Jan 1, 1985 to Dec 31, 2013, with English language restriction, using the search terms “gestational diabetes”, “diabetes mellitus”, “type 2 diabetes mellitus”, “early progression”, “early postpartum”, “postpartum”, “risk factors”, “predictors”, we identified 13 retrospective and prospective cohort studies compatible with the goal of our review. In total the 13 studies included 4970 women. The main characteristics of the studies and the identified risk factors are schematically shown in table 1 [19-31]. Most studies were published before 2010. Follow up ranged from 6 weeks to 1 year postpartum and most studies evaluated a mixed ethnic population. The prevalence of diabetes and glucose intolerance postpartum varied widely from 18% to 60%.

When interpreting the results of the 13 included studies, we faced a couple of difficulties that also trouble more generally the whole literature on GDM. Firstly, many different diagnostic criteria are used for GDM and postpartum T2DM/impaired glucose intolerance and thus studies identify women with different underlying degrees of glucose intolerance. Secondly, there are only a limited number of recent studies. Data from older studies are less

representative since the characteristics of the background population have changed due to the worldwide increase of obesity and T2DM. Thirdly, some of the older publications also include women with positive auto-immune antibodies and thus women at high risk of developing type 1 diabetes. Finally, many studies probably also included women with preexisting T2DM since universal screening for unknown overt diabetes in early pregnancy, as discussed before, was generally not done in the past.

The 13 studies identify almost the same long list of risk factors as mentioned above, but they all depict a different subset of risk factors as statistically significant. The most frequent statistically significant risk factors across all studies are maternal age, pre-pregnancy weight, early GDM diagnosis, insulin treatment during pregnancy and some biochemical risk factors such as the FPG on the diagnostic OGTT during pregnancy. Importantly, the only study that focused on the ethnic origin, clearly demonstrated a statistically significant difference in risk of progression to glucose intolerance between different ethnicities [23]. The ADA guidelines on screening postpartum for women with GDM can therefore not be blindly introduced worldwide, but should be evaluated in different ethnic populations and if needed be adapted accordingly. Another important comment is that the study of Retnakaran et al also demonstrated that any degree of abnormal glucose homeostasis in pregnancy, including milder glucose metabolism disturbances than GDM, independently predict an increased risk of glucose intolerance postpartum [27]. Therefore, the organization of some form of surveillance for these women might also be suggested.

Challenges to organize the postpartum follow up

Non-adherence to the postpartum screening strategy is a common problem. Postpartum follow-up screening rates for women diagnosed with GDM range from 16% to 58% within the first year postpartum, with only a part of these patients receiving an OGTT [32-47]. Annual follow up rates after the first year postpartum are often lower than 39% [36,38-40]. The barriers to postpartum diabetes testing are multifactorial, including a lack of time for a new mother to undergo diabetes testing, lack of knowledge of testing recommendations, failure of women to perceive themselves at high risk for diabetes, fragmentation of care between obstetricians and primary care providers and the perceived lack of efficacy of preventative measures by many clinicians [32, 40-42]. Challenges for primary care to organize this screening are also real, with the OGTT being a cumbersome and time-consuming test to organize [43].

The publication of clinical practice guidelines alone has been shown to be insufficient for improving postpartum screening [34,37]. The importance of postpartum screening should be highlighted in continuing education programs for health care workers and clinical practice guideline implementation initiatives. Implementation of case managers could be an option [44]. Introducing a local campaign with multidisciplinary meetings and mobilizing the general practitioners clearly improved the postpartum screening rates [45]. Several studies also demonstrated that installing an electronic system to trigger postpartum reminders with the use of postal reminders, SMS reminders or phone call reminders, helped to improve postpartum screening rates [46-49]. Furthermore, the National Gestational Diabetes Register in Australia has shown that postpartum rates increase up to 73% with the implementation of a local register system for women with GDM. This system encompasses the provision of information for women on GDM diagnosis and sends postpartum reminders to patients [50]. A comparable system is present in the Northern part of Belgium, the project 'Sweet Pregnant' (www.zoetzwanger.be). In this project women receive yearly remainders to have the FPG checked by their general practitioner. Since the start of the project 71% of women received at least once a FPG within three years of the diagnosis [51]. Finally, introducing an easier postpartum test than the OGTT will probably improve the screening uptake. Although the combination of a FPG and HbA1c has reasonable sensitivity, it clearly performs less well than an OGTT in early postpartum. Performing OGTTs in primary care might also be an option but this is often difficult to organize. A recent pilot study showed that a self-administered, capillary blood sampling OGTT device, was easy to use and the ability to test at home was well liked [52]. However, the reliability of the new technology still needs to be improved. When home OGTT testing kits become available on the market, this might become a good alternative to the in hospital OGTT.

The importance of postpartum screening for the prevention of T2DM

About 1 in 4 persons with T2DM are unaware of their disease. T2DM has a long asymptomatic phase, during which patients often already develop complications, such as background retinopathy or microalbuminuria. In consequence, at the time of diagnosis many patients with T2DM already have complications [1]. An early diagnosis and treatment of T2DM is therefore very important to prevent and treat diabetes related complications. Several high-quality randomized trials in patients with impaired fasting glucose or impaired

glucose tolerance show that lifestyle changes, including a 7% weight loss and a minimum of 150 minutes of physical activity weekly, resulted in a 58% reduction in the incidence of T2DM [53,54]. In the general population with prediabetes, treatment with metformin reduced the incidence of T2DM with 31% [54]. In women with a history of GDM, intensive lifestyle or metformin have both shown to delay or prevent T2DM in 50% of women. These interventions can easily be implemented in a primary care setting [5]. Primary care providers have therefore a key role in organizing the postpartum screening strategy, to increase the awareness of these women on their high risk of progression to T2DM and to timely start treatment.

Conclusion

Women with GDM are at increased risk of progression to glucose intolerance and T2DM in early postpartum. Appropriate follow up in early postpartum is an important opportunity in this high-risk population to timely detect glucose intolerance. This way, lifestyle interventions and if needed also metformin treatment, can be started to prevent or delay the development of diabetes. Evaluation of studies specifically analyzing the most important risk factors for progression in early post-partum, identified maternal age, pre-pregnancy weight, early GDM diagnosis, insulin treatment during pregnancy, some specific ethnicities and the FPG on the diagnostic OGTT during pregnancy as the most important risk factors. Primary care providers have a key role in organizing the postpartum screening strategy and to increase the awareness of these women on their high risk of progression to T2DM.

Article	Article information	Ethnic origin	Total GDM women	DM, AGM	Mean follow-up	GDM criteria	Definition of T2DM	Risk Factors (significant after multivariate logistic regression)
Metzger et al. [19]	Prospective 1985 Chicago	Mixed	113	38% DM 19% AGM	1 yr	NDDG, 1979	NDDG, 1979 with local adaptation (100g OGTT)	-maternal age -FPG -2h antepartum OGTT glucose -specific measure of β-cell function
Greenberg et al. [20]	Retrospective 1995 California	Mixed	94	16% DM 18% AGM	6 w	Second GDM Workshop Conference	NDDG, 1979	-history of GDM -insulin treatment during pregnancy -50g GCT ≥ 200mg/dL -any 2h postprandial glucose ≥ 150mg/dL
Buchanan et al. [21]	Prospective 1998 Los Angeles	Latino	122	10% DM 50% AGM	1-6 m	Third GDM Workshop Conference	ADA, 1997	For postpartum DM -AUC_g antepartum 100g OGTT -specific measure of β-cell function For postpartum AGM -early GDM diagnosis -weight gain -specific measure of β-cell function
Äberg et al. [22]	Prospective 2001 Sweden	White	229	9% DM 22% AGM	1 yr	EASD, 1991	WHO, 1985	-maternal age -insulin treatment during pregnancy -2h antepartum OGTT glucose
Sinha et al. [23]	Retrospective 2002 UK	Mixed	221	18% DM/AGM	6-12w	WHO, 1985	ADA, 1997	-ethnic origin -insulin treatment during pregnancy
Schaefer-Graf et al. [24]	Retrospective 2002 Los Angeles	Mixed	1636	14% DM 26% AGM	1-4m	Third GDM Workshop Conference	NDDG, 1979	For postpartum DM -earlier GDM diagnosis -history of GDM -FPG -AUC_g antepartum OGTT -1h antepartum OGTT glucose

Jang et al. [25]	Prospective 2003 South Korea	Asian	311	15% DM 23.2% AGM	6-8w	Third GDM Workshop Conference	WHO, 1985	For postpartum DM -pre-pregnancy weight -earlier GDM diagnosis -2h antepartum OGTT glucose -3h antepartum OGTT insulin For postpartum AGM: -pre-pregnancy weight -2h antepartum OGTT glucose -1h antepartum OGTT insulin
Rivas et al. [26]	Prospective 2007 Venezuela	Latin	117	46% DM/AGM	2-4m	Third GDM Workshop Conference	ADA, 1997	-earlier GDM diagnosis -insulin treatment during pregnancy -FPG -2h antepartum OGTT hyperglycemia
Retnakaran et al. [27]	Prospective 2008 Canada	Mixed	137	33% DM/AGM	3m	NDDG, 1979	CDA, 2003	-AUC_g antepartum OGTT -specific measure of insulin resistance
Retnakaran et al. [28]	Prospective 2010 Canada	Mixed	325 any degree of gestational dysglycaemia (not only GDM), but NGT on OGTT at 3-month postpartum)		1y	NDDG, 1979	CDA, 2003	For early progression to DM/AGM, after a normal OGTT at 3m postpartum -degree of glucose disturbance in pregnancy -glucose-related measures during OGTT 3m postpartum (AUC_g , delayed blood glucose peak, i.e.> 30min postload) -BMI, triglycerides 3m postpartum
Kim et al. [29]	Prospective 2011 Korea	Asian	381	5.2% DM 44.8% IGT	6-12m	Carpenter and Coustan	ADA, 2004	-family history of diabetes -BMI antepartum and postpartum -energy and fat intake postpartum -serum triacylglycerols postpartum -HbA1c postpartum -specific measure of β-cell function antepartum and postpartum
Kwak et al. [30]	Prospective 2013	Asian	843	12% DM at 2m	1yr for the	Third GDM Workshop	ADA, 2012	Early converters: -pre-pregnancy BMI

	Korea				majority of the cohort	Conference		-AUC_g antepartum OGTT -specific measure of β-cell function -CDKN2A/2B and HHEX gene
Benhalima et al. [31]	Retrospective 2014 Belgium	Mixed	215	5.3% DM 39.1% AGM	3m	Carpenter and Coustan	ADA, 2014 [1]	-specific measure of β-cell function antepartum and postpartum -insulin sensitivity postpartum

Table 2: Overview of studies evaluating risk factors for glucose intolerance in early postpartum

GDM: gestational diabetes; DM: diabetes; AGM: abnormal glucose metabolism (= any form of glucose intolerance except DM); IGT: impaired glucose tolerance; FPG: fasting plasma glucose; GCT: glucose challenge test; OGTT: oral glucose tolerance test;, AUC_g: area under the glucose curve; BMI: body mass index; w: weeks; m: months; yr: year; NDDG: National Diabetes Data Group; WHO: World Health Organization; EASD: European Association for the Study of Diabetes; CDA: Canadian Diabetes Association

Authors' contributions

LL and KB evaluated all the studies and wrote the review. JW, RD, JV and CM have been involved in revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Competing Interests

There are no competing interests of this manuscript for neither of the authors.

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