PRIMARY CARE DIABETES XXX (2018) XXX–XXX

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Delivery of an LGA infant and the maternal risk of diabetes: A prospective cohort study

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ARTICLE INFO

Article history:
Received 11 September 2017
Received in revised form
5 April 2018
Accepted 7 April 2018
Available online xxx

Keywords:
Gestational diabetes mellitus
Type 2 diabetes
Prediabetes
Large-for-gestational-age
Birth weight

ABSTRACT

Aims: Was to determine whether the birth weight of the infant predicts prediabetes (impaired fasting glucose, impaired glucose tolerance, or both) and type 2 diabetes (T2DM) during long-term follow-up of women with or without gestational diabetes mellitus (GDM).
Methods: The women with or without GDM during their pregnancies in Kuopio University Hospital in 1989–2009 (n = 876) were contacted and invited for an evaluation. They were stratified into two groups according to the newborn's birth weight: 10–90th percentile (appropriate-for-gestational-age; AGA) (n = 662) and >90th percentile (large-for-gestational-age; LGA) (n = 116). Glucose tolerance was investigated with an oral glucose tolerance test after a mean follow-up time of 7.3 (SD 5.1) years.
Results: The incidence of T2DM was 11.8% and 0% in the women with and without GDM, respectively, after an LGA delivery. The incidence of prediabetes increased with offspring birth weight categories in the women with and without GDM: from 46.3% and 26.2% (AGA) to 52.9% and 29.2% (LGA), respectively.
Conclusions: GDM women with LGA infants are at an increased risk for subsequent development of T2DM and therefore represent a target group for intervention to delay or prevent T2DM development. In contrast, an LGA delivery without GDM does not increase T2DM risk.

1. Introduction

Women with gestational diabetes mellitus (GDM) have an increased risk of both adverse obstetrical outcomes, mainly

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https://doi.org/10.1016/j.pcd.2018.04.002

Please cite this article in press as: H. Hakkarainen, et al., Delivery of an LGA infant and the maternal risk of diabetes: A prospective cohort study, Prim. Care Diab. (2018), https://doi.org/10.1016/j.pcd.2018.04.002

related to a large birth size of the newborn and subsequent development of type 2 diabetes (T2DM) [1–4]. GDM pathophysiology consists of insulin resistance accompanied by impaired β-cell function leading to maternal hyperglycemia [5]. Consequently, increased placental glucose transfer to the fetus causes fetal hyperinsulinemia and further macrosomia [6]. The underlying and worsening β-cell dysfunction coupled with a background of chronic insulin resistance usually due to overweight or obesity exposes a woman to an increased risk of developing diabetes. In clinical practice, a woman who delivers a large-for-gestational-age (LGA, birth weight above the 90th percentile for gestational age) infant is more likely to have GDM and this combination is considered a risk factor for GDM in a subsequent pregnancy. However, studies focusing on T2DM risk in women with a history of LGA birth (but without GDM) have given conflicting results, probably due to the variation of the follow-up time, ascertainment of the cases and controls and women's overall T2DM risk profile [7–10].

In other words, based on the pathophysiology of prenatal growth of LGA newborns, women with a history of an LGA infant delivery could be at an increased risk of subsequent development of diabetes. To test this hypothesis, our objective was to compare the incidence of subsequent prediabetes and T2DM in women with GDM to women without GDM in different birth size groups.

2. Methods

This hospital register-based cohort study included women whose pregnancies were treated in Kuopio University Hospital, Finland, in 1989–2009. Women who had the diagnosis of GDM and a random sample of normoglycemic control women, both groups with completed oral glucose tolerance test (OGTT) during pregnancy, were contacted by a letter and invited for the study. A total of 489 women with GDM and 385 controls with a normal OGTT result during pregnancy attended the follow-up study. 1234 women did not reply or refused to participate in the study. All participants gave a written informed consent.

The women with and without GDM were classified based on the birth weight of the newborn: between 10–90th percentile (appropriate-for-gestational-age; AGA) (n = 662) and over 90th percentile (LGA) (n = 116). The women without GDM and delivering a child with birth weight between 10-90th percentile served as a control group. In this study, LGA was defined as sex-specific birth weight for gestational age above the 90th percentile of the current Finnish newborn growth charts [11].

2.1. *Data collection during pregnancy*

In Finland, cost-free maternity care is offered to all pregnant women. The women considered to be at risk of GDM underwent 2-h OGTT (75 g glucose after overnight fasting) between the 24th and 28th weeks of gestation if one or more following factors were present: age over 40 years, BMI $\geq 25\,kg/m^2$, prior GDM or a delivery of a macrosomic infant, glucosuria, suspected fetal macrosomia in the current pregnancy. The diagnostic criteria of GDM were as follows: until September 2001 the lower limits of abnormal fasting, 1-h and 2-h capillary whole-blood glucose 4.8, 10.0 and 8.7 mmol/l and since September 2001 the lower limits of fasting, 1-h and 2-h capillary plasma glucose 4.8, 11.2 and 9.9 mmol/l as per contemporary guidelines. For the women with more than one delivery during the study period, the first pregnancy with an abnormal OGTT result was selected as the index pregnancy. The women with GDM were seen regularly in the Prenatal Outpatient Clinic in Kuopio University Hospital and they received dietary advice, regular blood glucose monitoring and insulin treatment when necessary. The hospital register included data on maternal characteristics and pregnancy risk factors, complications, pregnancy outcome, and on the neonatal period of the offspring. The women with overt T2DM at the time of pregnancy or T1DM diagnosed after the index pregnancy, and those with a multiple pregnancy were excluded to eliminate confounding factors.

2.2. *The follow-up study*

The participants were recruited to the follow-up study between 2006 and 2009. The women underwent laboratory tests, body composition and blood pressure measurements, and answered to a questionnaire concerning their family history and health behavior. To study glucose tolerance, the participants underwent 2-h OGTT (75 g of glucose). T2DM was defined according to the American Diabetes Association (ADA) recommendations: fasting plasma glucose ≥7 mmol/l or 2-h plasma glucose ≥11.1 mmol/l. Fasting plasma glucose between 5.6 and 6.9 mmol/l was defined as impaired fasting plasma glucose (IFG) and 2-h plasma glucose between 7.8–11.0 as impaired glucose tolerance (IGT) [12]. Women who had been diagnosed with T2DM during the follow-up time (N = 15) did not undergo OGTT.

Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared. Waist circumference (at the midpoint between the lateral iliac crest and the lowest rib) was measured to the nearest 0.5 cm.

2.3. *Laboratory determinations*

Plasma glucose was measured by an enzymatic hexokinase photometric assay (Konelab Systems reagents; Thermo Fischer Scientific, Vantaa, Finland), insulin by an immunoassay (ADVIA Centaur Insulin IRI no. 02230141; Siemens Medical Solutions Diagnostics, Tarrytown, NY), and HbA1c by a high-performance liquid chromatography assay (TOSOH G7 glycohemoglobin analyzer, Tosoh Bioscience, Inc., San Francisco, CA), calibrated to direct-current current transformers (DCCT) standard.

2.4. *Statistical analyses*

The statistical analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL). The results were given as the mean ± SD or number of cases and percentages. Statistical differences in categorical variables between the study groups and controls were evaluated using the χ^2 test. Anthropometric and biochemical continuous variables were analyzed using Student's t-test, and log-transformed variables were

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