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Primary Care Diabetesjournal 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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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.

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1. Introduction

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

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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, $BMI \geq 25 \text{ kg/m}^2$, 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 capil-

lary 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 Out-patient 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 $\geq 7 \text{ mmol/l}$ or 2-h plasma glucose $\geq 11.1 \text{ mmol/l}$. 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 \pm 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

Table 1 – Prepregnancy and peripartum characteristics of the study subjects stratified according to the birth weight of the offspring.

Offspring's birth weight	AGA (10–90 percentile)		LGA (>90 percentile)	
	Mean ± SD or %		Mean ± SD or %	
	No GDM	GDM	No GDM	GDM
Number of subjects	(Controls) 286	(Group 1) 376	(Group 2) 48	(Group 3) 68
Prepregnancy characteristics				
Age (years)	29.5 ± 5.4	31.8 ± 6.0**	30.6 ± 5.0	32.6 ± 6.3**
Prepregnancy BMI (kg/m ²)	23.8 ± 3.8	26.4 ± 5.0**	25.7 ± 3.5*	26.7 ± 4.1**
Primiparity (%)	54.4	37.8**	33.3*	22.1**
Family history of diabetes (%)	69.4	81.4**	75.0	80.6
Not married (%)	34.3	40.4	29.2	29.4
Smoking (>5 cigarettes/day) (%)	15.2	21.5*	12.8	18.5
Alcohol consumption (%)	47.2	40.2	34.0	52.3
Prior child's birth weight >4000 g (%)	25.4	25.6	43.8*	60.4**
Prior spontaneous abortion (%)	16.8	19.9	18.8	35.3*
Prior cesarean section (%)	5.9	9.6	16.7*	7.4
Peripartum characteristics of the subjects and newborns				
Weight gain in pregnancy (kg)	13.7 ± 4.8	11.8 ± 5.9**	14.7 ± 4.7	14.9 ± 6.1
Gestational age (day)	280 ± 11	278 ± 11*	279 ± 11	279 ± 8
Pre-eclampsia (%)	1.4	5.3*	2.1	5.9*
Female offspring (%)	47.2	43.6	47.9	55.9
Birth weight (g)	3595 ± 385	3596 ± 406	4365 ± 424**	4421 ± 370**
Placental-fetal mass ratio (%)	17.1 ± 3.0	17.5 ± 3.0	20.6 ± 15.8**	17.9 ± 2.5*
Apgar score <7 at 1 min (%)	1.7	5.9*	6.3	4.4

GDM = gestational diabetes mellitus, BMI = body mass index, AGA = appropriate for gestational age; LGA = large for gestational age.

All groups compared to controls separately.

* $p < 0.05$.

** $p < 0.0001$.

used to correct for their skewed distribution when appropriate. $p < 0.05$ was considered statistically significant. Since the diagnosis of GDM was based on slightly different criteria depending on the origin of the blood during the data collection, a correlation coefficient was used to convert all values to correspond venous plasma levels. The correlation coefficient was based on the information from the Department of Clinical Chemistry at Kuopio University Hospital.

This study was approved by the local Ethics Committee of the Kuopio University Hospital in accordance with the Helsinki Declaration.

3. Results

The prepregnancy and peripartum characteristics of the women with and without GDM stratified according to the birth weight of the offspring are shown in Table 1. The women with previous GDM were older and heavier in both birth weight categories than those without GDM. Parity was higher in the women with GDM and in those with an LGA delivery without GDM. The women with GDM in the AGA group had more diabetes in family history and smoked more often. Otherwise, the study groups had comparable family history of diabetes, marital, smoking and alcohol consumption status. Prior spontaneous abortion rate was higher in the women with GDM in the LGA group. The women with LGA infants had more frequently a history of a macrosomic offspring

than those in the normal birth weight groups. However, prior cesarean section was more common in the women with LGA infants and absence of GDM. The women with GDM in the AGA group gained less weight during pregnancy, had shorter gestational age and lower Apgar score at delivery than the controls. The incidence of pre-eclampsia was higher in both GDM groups compared to controls. No significant difference was observed in the gender of the offspring between the subgroups.

The clinical characteristics of the study groups at the follow-up study are shown in Table 2. The women with GDM had shorter follow-up time in both birth weight categories. As during the index pregnancy, the women with GDM were significantly heavier in both birth weight categories. However, the groups did not differ in weight gain during the follow-up time. The GDM women had higher basal glucose and insulin levels in both birth weight groups.

The incidence of prediabetes (IFG and/or IGT) and T2DM at the follow-up study according to the birth weight of the offspring is shown in Fig. 1. During the follow-up time after the index pregnancy, the incidence of prediabetes increased in the women with and without GDM from 46.3% and 26.2% (AGA) to 52.9% and 29.2% (LGA). The incidence of T2DM was 11.8% in the GDM women and 0% in the women without GDM who had given birth to LGA infants. The incidence of T2DM in the GDM women with previous LGA delivery was significantly higher compared to the GDM women with AGA delivery as well.

Table 2 – Clinical characteristics and glucose tolerance data of the study subjects at the follow-up study.

Offspring's birth weight	AGA (10–90 percentile)		LGA (>90 percentile)	
	Mean ± SD or n (%)		Mean ± SD or n (%)	
	No GDM	GDM	No GDM	GDM
Number of subjects	(Controls)	(Group 1)	(Group 2)	(Group 3)
Follow-up time (years)	286	376	48	68
Age at follow-up (years)	8.5 ± 5.5	5.3 ± 4.3 ^{**}	7.4 ± 5.4	6.2 ± 4.9 [*]
BMI (kg/m ²)	38.4 ± 6.4	37.4 ± 7.2	38.3 ± 5.8	39.1 ± 7.5
Weight gain during follow-up time (kg)	26.5 ± 4.9	28.3 ± 5.7 ^{**}	27.9 ± 4.8 [*]	29.2 ± 4.9 ^{**}
HbA1c (mmol/mol)	5.7 ± 7.6	3.6 ± 7.9	4.3 ± 7.6	5.6 ± 9.3
Fasting plasma glucose (mmol/l)	35.0 ± 3.2	35.9 ± 4.8 [*]	34.8 ± 3.5	38.4 ± 6.6 ^{**}
30-min plasma glucose (mmol/l)	5.3 ± 0.4	5.6 ± 0.8 [*]	5.4 ± 0.4	5.8 ± 0.8 ^{**}
2-h plasma glucose (mmol/l)	7.0 ± 1.5	7.9 ± 1.7 ^{**}	7.1 ± 1.3	8.1 ± 1.7 ^{**}
Fasting plasma insulin (mU/l)	5.5 ± 1.2	5.9 ± 1.6 ^{**}	5.5 ± 1.0	6.6 ± 2.4 ^{**}
30-min plasma insulin (mU/l)	9.0 ± 6.6	11.7 ± 9.0 ^{**}	8.0 ± 4.6	12.4 ± 7.3 ^{**}
2-h plasma insulin (mU/l)	62.6 ± 38.9	72.5 ± 49.8 [*]	57.6 ± 29.2	78.2 ± 59.8
Prediabetes	75 (26.2)	174 (46.3) ^{**}	14 (29.2) ^a	36 (52.9) ^{**}
T2DM	1 (0.3)	17 (4.5) [*]	0 (0)	8 (11.8) ^{*,b}

GDM = gestational diabetes mellitus, BMI = body mass index, AGA = appropriate for gestational age, LGA = large for gestational age.

All groups compared to controls separately.

* p < 0.05.

** p < 0.0001.

^a Significantly (p < 0.05) different when comparing groups 1 and 2.

^b Significantly (p < 0.05) different when comparing groups 1 and 3.

4. Discussion

This prospective long-term study of the women with and without GDM demonstrated that a history of an LGA infant in the absence of GDM did not predict T2DM. In contrast, 11.8% of the women with GDM and LGA infants developed T2DM during a ten-year follow-up. Moreover, the incidence of prediabetes was significantly greater in the GDM women in both birth weight categories; every other woman had prediabetes in the follow-up. Only one of four women without GDM had prediabetes when the infant's birth weight was between 10–90th percentile. Overall, the delivery of an LGA infant is predictive of maternal long-term outcomes in women with GDM but not in women with normal glucose tolerance during pregnancy.

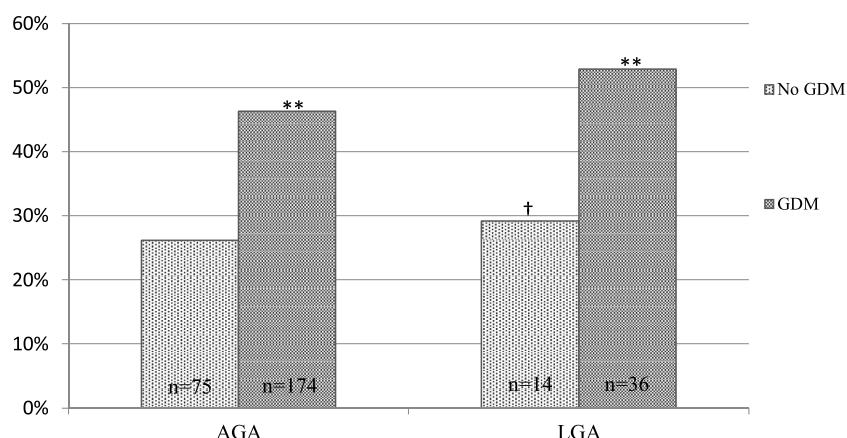
The well-known Pedersen hypothesis (1952) states that maternal hyperglycemia causes macrosomia through fetal hyperglycemia and hyperinsulinemia [6]. To date, however, it is known that a variety of factors affects infant's birth weight, such as high parity and prepregnancy overweight [13]. Especially maternal BMI has much higher impact on the prediction of an LGA delivery than the 2-h glucose level in OGTT during pregnancy [14]. This opens up a wider viewpoint reflecting the reasons behind an LGA delivery and, thus, for the consequences of an LGA delivery to the women's long-term health.

Infrequent studies exist on the association between an LGA delivery and subsequent maternal T2DM. In these studies, settings, follow-up times, ascertainment of cases and controls and LGA definitions vary substantially. To elucidate this complex ground, we performed a literature search and collected the appropriate data to Table 3. Contrary to our study, the review suggests that the risk of T2DM after an LGA deliv-

ery is somewhat increased: pooled OR 1.26 (95% CI 0.97–1.63). Taking into account available adjusted ORs, the risk became significant: pooled OR 1.37 (95% CI 1.14–1.65) (Table 3). There appeared to be a few factors affecting the results. Up to 27 years postpartum, Larsson et al. demonstrated that the incidence of T2DM had risen but this was explained by obesity and high parity [7]. Tehrani et al. included also stillbirths in the LGA study group which could have affected the results [8]. Moreover, two studies included GDM women in the study groups [15,16], biasing the results, whereas GDM status was carefully defined and checked in the present study. In fact, these two studies [15,16] along with the Larsson et al.'s study [7] were the only studies suggesting significantly increased T2DM risk after an LGA delivery. The remaining previous studies [8,10], and our findings did not demonstrate significantly increased risk of later T2DM. In addition, a study of 18 women with LGA compared to 18 women with appropriate-for-gestational-age (AGA) infants did not find significant differences in glucose, insulin or HbA1c levels between the groups two years after pregnancy [9]. Taking together, the predictability of later T2DM after an LGA delivery depended on various factors in study settings.

The present study demonstrated that GDM women with a previous LGA delivery have a considerable risk for incident T2DM. We identified a few factors associating with an LGA delivery in the GDM women; they were older and heavier in prepregnancy, had higher parity and probably severer dysglycemia during pregnancy than the GDM women without an LGA delivery. In a previous study, we have demonstrated that women with two or more abnormal values in OGTT during pregnancy are at an increased risk for the development of T2DM [4]. Despite the fact that all the women in this study had one or more risk factors for GDM, an LGA delivery in women

The incidence of prediabetes



The incidence of T2DM

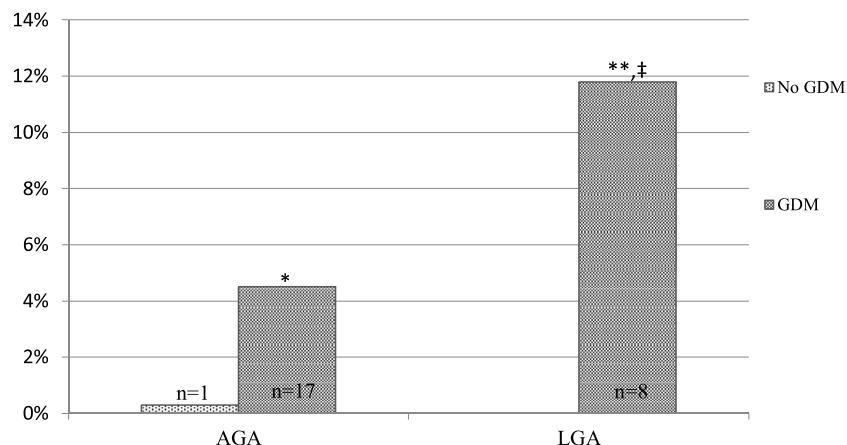


Fig. 1 – The incidence of glucose intolerance among the study groups at the follow-up according to the birth weight of the newborn.

GDM = gestational diabetes mellitus, T2DM = type 2 diabetes mellitus, AGA = appropriate for gestational age, LGA = large for gestational age.

* $p < 0.05$, ** $p < 0.0001$ when comparing all groups separately to women without GDM in AGA group.

†Significantly ($p < 0.05$) different when comparing women without GDM in LGA group to women with GDM in AGA group.

‡Significantly ($p < 0.05$) different when comparing women with GDM in LGA group to women with GDM in AGA group.

without GDM did not predict later T2DM. This was an interesting finding since despite clinical risks brought about by an LGA delivery and being overweight, these women clearly had some potential protective factors against T2DM.

The strengths of the current study included the long-term follow-up of a well-characterized cohort of women, and the similar treatment received by all participants with GDM during pregnancy. It should be noted that in the present study, the GDM criteria in years 1989–2008 were tight especially regarding the fasting glucose value in OGTT. Consequently, our results indicated that the absence of T2DM in women with an LGA delivery but without GDM was genuine. The limitations of this study involved the inclusion of subjects based on a risk-based screening, which may have caused some selection bias.

In addition, the study setting was cross-sectional at the time of follow-up OGTT, not longitudinal that would have been optimal to standardize the protocol.

5. Conclusion

We conclude that GDM women with LGA infants are at increased risk for the subsequent development of T2DM and therefore represent a target group for intervention to delay or prevent development of T2DM. However, the findings also implied that an LGA delivery in the absence of GDM does not predict T2DM in the mean follow up time of 7.3 years. Thus,

Table 3 – Summary of studies on the association between a delivery of an LGA infant and the risk of incident T2DM.

Studies by follow up time	Follow-up time	LGA definition	Number of cases/ controls	BMI (kg/m ²) cases/ controls mean(SD)	Outcome	Outcome incidence in cases/ controls % or mean(SD)	adjusted OR (95% CI)	unadjusted OR (95% CI)	p	Pooled OR adjusted + unadjusted (95% CI)	Pooled OR unadjusted (95% CI)
Kew et al., Canada [10]	3 months	>90th percentile	62/364	24.7/25.4	Prediabetes or T2DM	15.2/9.1%	1.7 ^a (0.70–4.10)	1.79 (0.82–3.91)	–	1.37 (1.14–1.65) <i>p</i> <0.001	1.26 (0.97–1.63) <i>p</i> =0.085
Moses et al., Australia [9]	2 years	>90th percentile	18/18	25.0 (4.0)/24.6 (3.1)	fasting glucose (mmol/l) HbA1c (%)	4.5 (0.4)/4.6 (0.5) 5.0 (0.4)/5.2 (0.4)	–	–	NS	NS	NS
Kabeya et al., Japan ^d [15]	5 years	>4 kg	405/6406	24.3 (3.1)/23.7 (3.1)	T2DM	6.8/4.6%	1.24 ^b (0.80–1.94)	1.51 (1.01–2.27)	–	–	–
Tehrani et al., Iran ^e [8]	9 years	>4 kg	570/570	30.5 (4.8)/30.7 (5.1)	T2DM	9.5/11.1%	–	0.84 (0.57–1.23)	NS	–	–
James-Todd et al., UK ^d [16]	22 years	>4.5 kg	654/41 292	23.8 (4.4)/–	T2DM	–	aHR 1.61 ^c (1.24–2.08)	–	–	–	–
Larsson et al., Sweden [7]	20–27 years	>4.5 kg	236/382	BMI ≥ 27 48.7/20.2%	T2DM	4.7/0.8%	–	6.12 (1.71–21.93)	0.002	–	–

^a Adjusted for age, months' postpartum, ethnicity, family history of diabetes, breastfeeding, and waist circumference.

^b Adjusted for age, BMI, systolic BP, family history of diabetes and daily walking time.

^c Adjusted for maternal age at first birth, age in 1989, race/ethnicity, pre-pregnancy BMI, family history of diabetes, menstrual irregularity, smoking during pregnancy, history of gestational diabetes mellitus, history of hypertensive disorders of pregnancy.

^d The studies include GDM patients.

^e The LGA study group includes stillbirths, T2DM = type 2 diabetes mellitus, BMI=body mass index, OR=odds ratio, HR=hazard ratio.

an LGA delivery in non-GDM women is likely to be related to other factors than maternal dysglycemia.

Conflict of interest

The authors state that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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