# High risk of neonatal complications in children of mothers with gestational diabetes mellitus in their first pregnancy

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## ABSTRACT

**INTRODUCTION:** The study presents the neonatal outcome from a cohort of women with gestational diabetes mellitus (GDM) in their first pregnancy.

**METHODS:** During a five-year period (2009-2013), a prospective follow-up study was performed at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital – Kolding. The study included 535 pregnant women diagnosed with GDM. A study population of nulliparous GDM patients was sampled, and during the period from 1 January 2010 to 1 March 2013, a total of 137 women delivered for the first time. The present study population considers the 131 offspring, excluding six pairs of twins.

**RESULTS:** The overwhelming majority of the offspring had a birth weight within the normal range and only six (4.6%) were large for gestational age. There were 95 (72.5%) vaginal deliveries, whereas 36 (27.5%) were born by caesarean section (CS). Nearly half of the 25 nulliparous GDM patients with a body mass index ≥ 35 kg/m² delivered by CS – six by emergency CS and three by planned CS. A total of 20 neonates (15.3%) developed neonatal hypoglycaemia and four (3.1%) had an Apgar score < 7 after 5 min. A total of 25 (19.1%) among the offspring were admitted to the neonatal intensive care unit.

**CONCLUSION:** The present study supports the notion of high-risk pregnancy among GDM patients. Compared with nulliparous in general, the offspring were more likely to be delivered by emergency CS. Despite the prophylactic procedures, one in six had neonatal hypoglycaemia.

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**TRIAL REGISTRATION:** not relevant.


The present paper considers the offspring of a mother diagnosed with gestational diabetes mellitus (GDM), and the study population is thus defined by the maternal condition. It is motivated by the growing evidence of the implications for the offspring of the intrauterine environment and the neonatal period, referring to the concepts First 1000 Days and the concept Developmental Origins of Health and Disease (DOHaD) [1].

GDM is defined as carbohydrate intolerance with onset or first recognition during pregnancy [2]. GDM increases the risk of various complications in pregnancy and delivery [3-5]. Furthermore, the intrauterine exposure to maternal glucose intolerance places the offspring at an increased risk for long-term adverse outcomes [6, 7].

In Denmark, a screening program has been implemented as part of public antenatal care [8, 9]. Accordingly, pregnant women who are considered to be at risk are offered a 75-g 2-h oral glucose tolerance test (OGTT). Subsequently, the GDM patient is invited to participate in a special antenatal care programme.

This study presents the neonatal outcome of a regional cohort of nulliparous GDM patients who were treated with diet only.

## METHODS

### Screening for gestational diabetes mellitus

In accordance with the Danish routine screening procedure for GDM, pregnant women with glycosuria and/or prior GDM, a pre-pregnancy body mass index (BMI) ≥ 27 kg/m², a family history of diabetes and previous offspring birth weight above 4,500 g are invited to have a 75-g oral glucose tolerance test (OGTT) [8, 9]. GDM is diagnosed if the blood glucose level is ≥ 9.0 mmol/l after 2 h. In the present context, all tests were performed at the hospital laboratory in accordance with a standardised procedure.

### The study population

During a five-year period (2009-2013), 15,735 women gave birth at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital - Kolding [9]. Among them a cohort was established of the 535 pregnant women who had been diagnosed with GDM, corresponding to a 3.4% incidence.

The GDM patients were to follow a special antenatal care programme with individual nutritional counselling and dietary advice, introducing a calorie-restricted, low-carbohydrate diet. They were offered an initial consultation with an obstetrician giving information on GDM, providing a range of clinical examinations and an ultrasonographic measurement in order to follow foetal growth. The GDM patients returned for follow-up visits at intervals of 2-6 weeks throughout their pregnancy.

ORIGINAL ARTICLE

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Large or small for gestational age at birth – the influences of the intrauterine environment?

Depending on the circumstances, the health-care professional at the consultation could be a specialised diabetic nurse, an obstetrician or a dietician. Supervision by an endocrinologist was always possible. In total, 24 (4.4%) of the GDM patients presented blood glucose levels and/or $HbA_{1c}$ values exceeding the treatment goals, which were a self-monitored blood glucose level of 4-6 mmol/l pre-prandially and 4-8 mmol/l post-prandially measured in profiles at least twice a week and an $HbA_{1c}$ < 5.6% [8]. These patients were insulin-treated and subsequently excluded from the present cohort. Regarding childbirth, if delivery was not the result of spontaneous labour, the delivery was induced at term or if the estimated foetal size exceeded 4,000 g.

The infants eligible for inclusion in the present study were the offspring of nulliparous women diagnosed with GDM before their 34th gestational week who gave birth at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital – Kolding, during the period from 1 January 2010 to 1 March 2013. The study was a follow-up study addressing breastfeeding and the growth pattern among the infants and young children. The study period was defined in order to select children between six and 36 months of age, because the study was a follow-up study addressing breastfeeding and the growth pattern among the infants and young children.

Hence, the study population consisted of the offspring of 131 singleton pregnancies, excluding the six pairs of twins.

**Data**

Data on the cohort of GDM patients were collected prospectively and stored in a computerised database. All pregnant women had an ultrasonographic examination at their 12th week of gestation defining gestational age (GA) [9]. GA at first visit was recorded. The indication for OGTT was recorded as well as the value. The pre-pregnancy Body Mass Index (BMI) was calculated using the weight and the height observed by the general practitioner at first visit in the antenatal care programme, which usually takes place before the tenth gestational week. Furthermore, data included a range of variables including the delivery, the pregnancy outcome and the post-partum follow-up OGTT.

To limit the amount of typing errors, all data were recorded twice and subsequently compared and corrected.

The present analyses consider data on pre-pregnancy BMI and the mode of delivery, the birth weight, Apgar score at 5 min., admission to the Neonatal Intensive Care Unit (NICU) and the neonate's blood sugar 2 h after birth (neonatal hypoglycaemia). The recorded birth weight was related to GA at birth using Astraia software. Hence, the new-born infant was categorised as small for GA (SGA), defined as birth weight deviating –2 SD (standard deviations) or –22%, large for GA (LGA) defined as a birth weight deviating +2 SD or +22%, or appropriate for GA (AGA).

Data were subsequently transferred and analysed in SPSS Statistics version 22.

**Ethics**

At one of the obstetrical visits, the GDM patient was informed of the study in order to provide participation consent. No written consent of participation was collected. The study did not embrace biomedical research and consequently did not need assessment by the Danish Research Ethics Committee System. The Danish Data Protection Agency approved the protocol and the database.

*Trial registration:* not relevant.

**RESULTS**

No intrauterine or neonatal deaths were observed. Only eight (6.1%) infants were born preterm before GA 37 + 0. This is in line with the level observed among all nulliparous in Denmark in the same period [10].

There were 95 (72.5%) vaginal deliveries, while 36 (27.5%) were delivered by caesarean section (CS). The rate of emergency CS among nulliparous GDM patients was calculated to 22.2%. In comparison, the local rate of emergency CS among all nulliparous was 15.6% [10]. **Table 1** presents the mode of delivery in categories according to the maternal pre-pregnancy BMI. Compared with GDM patients with a pre-pregnancy BMI < 27 kg/m², a higher proportion of the overweight GDM patients delivered by CS - the frequency was significantly higher at the 0.10 level (chi squared = 0.0687; p = 0.793188).

**Table 2** considers the birth weight in relation to the maternal pre-pregnancy BMI. The overwhelming majority were AGA (n = 118; 90.1%). Only six (4.6%) neonates

were LGA and half of them were offspring of nulliparous GDM patients with a pre-pregnancy BMI ≥ 35 kg/m². Of the six LGA infants, three were delivered by CS. In total, seven neonates were SGA and five of them were offspring of mothers with a BMI < 27 kg/m².

A total of 25 neonates (19.1%) and slightly more than one in three (n = 10; 34.5%) of the neonates delivered by emergency CS were admitted to the NICU (**Table 3**). There were various indications for this, primarily prematurity, asphyxia, hypoglycaemia and respiratory distress. Due to the complexity of reasons, the present study does not provide conclusions on the specific indications for admission to the NICU. Among the 131 newborns, there were four (3.1%) with an Apgar score ≤ 7 after 5 min., and they were all admitted to the NICU. In comparison, among all nulliparous delivering at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital – Kolding, the admission rate to the NICU due to an Apgar score ≤ 7 after 5 min. was 0.9% [10].

In accordance with common guidelines, all the offspring of GDM patients were offered hypoglycaemic prophylaxis consisting of hypo-allergic formula delivered by cup, syringe, bottle and tube during the first hours of life. Subsequently, the blood glucose was checked by a capillary blood sample from the heel of the newborn after 2 h. In total, 20 (15.3%) of the 131 offspring were diagnosed with neonatal hypoglycaemia, defined as blood glucose < 2.5 mmol/l (Table 3). Two of whom had severe hypoglycaemia (< 1.5 mmol/l).

## DISCUSSION

A systematic review evaluating the consequences of foetal exposure to maternal hyperglycaemia reported methodological limitations of existing studies and proposed ideal designs for future studies, recommending a separation of pre-gestational diabetes and GDM [7]. In the present study, women with pregestational diabetes mellitus were not considered, and the GDM patients in need of insulin were excluded. Hence, the present study considers the offspring of mothers with pregnancy-related carbohydrate intolerance most likely due to other factors than undiagnosed pregestational diabetes or overt diabetes with first sign during pregnancy. Accordingly, the impact of a significant medical disorder can be ignored, a notion which is supported by the fact that the GDM patients managed to fulfill the treatment goal on diet only. The timing of foetal exposure to elevated maternal glucose levels is documented by the GA at inclusion; and for the present study population, this period was six weeks or longer. The maternal lifestyle during pregnancy is characterised by the calorie-restricted, low-carbohydrate diet, documented by the registered blood glucose and $HbA_{1c}$ levels. In an attempt to sample individuals with common characteristics, this study only included the offspring of nulliparous women. Hence, we eliminated confounders like history of previous GDM or macrosomia. Furthermore, nulliparous women can be assumed to be younger than samples of all pregnant women diagnosed with GDM. This criterion hence min-

**TABLE 1**

The mode of delivery presented in categories according to the maternal pre-pregnancy body mass index (BMI). The results consider the offspring of 131 nulliparous women diagnosed with gestational diabetes mellitus before their 34th gestational week and who gave birth to a singleton at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital – Kolding, during the period 1 January 2010 – 1 March 2013.

| BMI, kg/m² | Vaginal, n (%) | Planned caesarean section, n (%) | Emergency caesarean section, n (%) | Total, n (%) |
|---|---|---|---|---|
| < 27 | 42 | 2 | 13 | 57 |
| 27.0-34.9 | 37 | 2 | 10 | 49 |
| ≥ 35 | 16 | 3 | 6 | 25 |
| Total | 95 (72.5) | 7 (5.3) | 29 (22.2) | 131 (100.0 ) |

**TABLE 2**

The birth weight presented in categories according to the maternal pre-pregnancy body mass index (BMI). The results consider the offspring of 131 nulliparous women diagnosed with gestational diabetes mellitus before their 34th gestational week and who gave birth to a singleton at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital – Kolding, during the period 1 January 2010 – 1 March 2013.

| | Size for gestational age, n (%) | | | |
|---|---|---|---|---|
| BMI, kg/m² | small | appropriate | large | Total, n (%) |
| < 27 | 5 | 49 | 1 | 55 |
| 27.0-34.9 | 1 | 48 | 2 | 51 |
| ≥ 35 | 1 | 21 | 3 | 25 |
| Total | 7 (5.3) | 118 (90.1) | 6 (4.6) | 131 (100) |

**TABLE 3**

The neonatal outcome by mode of delivery among the 131 offspring of nulliparous women diagnosed with gestational diabetes mellitus before their 34th gestational week and who gave birth to a singleton at the Department of Gynaecology and Obstetrics, Lillebaelt Hospital – Kolding, during the period 1 January 2010 – 1 March 2013. The values are n.

| | Vaginal | Planned caesarean section | Emergency caesarean section | Total |
|---|---|---|---|---|
| Apgar score ≤ 7 | | | | |
| after 5 min. | 3 | 0 | 1 | 4 |
| Neonatal hypoglycaemia[a] | 13 | 1 | 6 | 20 |
| Admission to NICU | 14 | 1 | 10 | 25 |

NICU = Neonatal Intensive Care Unit.
a) Neonatal hypoglycaemia is defined as blood glucose concentration < 2.5 mmol/l measured within 2 h after delivery.

imised the possible impact of age on carbohydrate intolerance during pregnancy as well as on the pregnancy outcome in general. In the present study, twin pregnancies have not been considered as twins are often smaller and born earlier than singletons. Finally, other relevant confounders were addressed, such as pre-pregnancy BMI. In conclusion, the present study population represents the outcome of a pregnancy in which the intrauterine milieu may be considered well-described regarding a range of factors with a possible impact on the foetus, the neonate and, subsequently, for the development of later health and disease.

The overwhelming majority of the offspring had a birth weight within the normal range and only six were LGA. This is a noteworthy finding, and it is different from that of other reports [11-14]. The present study considered only first-time pregnancies and only pregnancies in which the GDM patient was able to control the blood glucose and $HbA_{1c}$ levels through diet only. Further, delivery was induced after the 37th gestational week if the estimated foetal weight exceeded 4,000 g. Both may explain the lower prevalence of LGA. However, the finding may also be interpreted as an attainable effect regarding the risk of having an "overweight newborn" by the intervention through a specific antenatal care programme, including control of the blood glucose values. This notion is supported by the perception of pregnancy-related carbohydrate intolerance as a continuum in which adverse outcomes increase concordantly with worsening hyperglycaemia [4, 13, 15].

Nevertheless, the findings in the present study support the notion of a high-risk pregnancy among GDM patients [5]. Slightly more than one in five of the offspring was delivered by emergency CS, and a considerable number of the newborns had an Apgar score < 7 at 5 min. Furthermore, despite careful prophylaxis, a high proportion of the offspring of nulliparous GDM patients – one in six or 14.1% – were diagnosed with neonatal hypoglycaemia. In the HAPO study, no significant correlation between the maternal plasma glucose level and neonatal hypoglycaemia was found, but the definition of neonatal hypoglycaemia in the study was different as it included values up to 24 h after birth [13]. In a comparable Danish study, only 4.1% of the offspring of GDM patients being able to fulfill the treatment goal regarding control of blood glucose values during pregnancy had neonatal hypoglycaemia [14]. The observed higher prevalence may be explained by the fact that the present study only encompasses nulliparous GDM patients, which suggests a longer mean duration of delivery and thus a possible impact on the level of the neonatal blood glucose.

The association between overweight and GDM is evident [16]. Overweight is considered a contributing risk factor to GDM and it has been pointed out that glucose intolerance in pregnancy encompasses the pathophysiology related to both insulin resistance and overweight and may even cover factors behind oxidative stress [17, 18]. Both GDM and overweight are associated with adverse pregnancy outcomes [13, 17, 19]. In summary, the association between overweight and GDM is of particular interest and focus should be extended also to include the offspring, their infancy and childhood [1]. In order to quantify the independent contribution of carbohydrate intolerance to maternal overweight, there is a need for further studies comparing overweight pregnant women with and without GDM to clarify the relationship between foetal growth, the delivery and the pregnancy outcome. The present study highlights the conditions of the overweight pregnant woman as the Danish public antenatal care programme invites pregnant women with a pre-pregnancy BMI ≥ 27 kg/m² or higher to have an OGGT [9]. Accordingly, more than half of the nulliparous GDM patients had a pre-pregnancy BMI ≥ 27 kg/m². The findings support the notion that it may be possible to influence foetal growth if the maternal blood glucose is well controlled during pregnancy. This suggests that an additive, beneficial effect of a calorie-restricted, low carbohydrate diet may be of significance. However, the neonatal complications still appear considerable, which emphasises that pregnant women diagnosed GDM should deliver in hospitals with a neonatal ward.

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