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Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? A prospective study

Isabelle Mortier¹ · Julie Blanc^{1,2} · Barthelemy Tosello^{3,4} · Catherine Gire³ · Florence Bretelle^{1,4} · Xavier Carcopino^{1,5}

Abstract

Purpose To evaluate if neonates delivered after 34^{0/7} weeks from mothers diagnosed with gestational diabetes (GD) are exposed to an increased risk of neonatal severe respiratory distress syndrome (SRDS).

Methods Women with singleton pregnancy in labour after 34^{0/7} weeks of gestation or admitted for planned caesarean section and who had been systematically screened for GD were eligible to participate to this prospective cohort study. Diagnosis of SRDS was defined by the association of clinical signs of early neonatal respiratory distress, with consistent radiologic features and requiring mechanical ventilation with a fraction of inspired oxygen (FiO₂) >0.25 for a minimum of 24 h and admission to neonatal intensive care unit.

Results A total of 444 women were included. GD was diagnosed in 60 patients (13.5%). A neonatal SRDS was diagnosed in 32 cases (7.2%). Compared to others, neonatal SRDS was significantly more often observed in neonates from women diagnosed with GD: 12 (20%) vs. 20 (5.2%),

respectively ($p < 0.001$). Women whose neonates presented neonatal SRDS were significantly more likely to be obese ($p = 0.002$), to have undergone a caesarean section ($p < 0.001$) and to have received corticosteroids therapy before 34^{0/7} weeks ($p = 0.013$). In multivariate analysis, GD was identified as an independent risk factor of neonatal SRDS (aOR 3.6; 95% CI 1.5–8.6; $p = 0.005$). Other risk factors were maternal obesity (aOR 2.8; 95% CI 1.1–7.1; $p = 0.029$) and assisted vaginal delivery (aOR 5.5; 95% CI 1.9–15.9; $p = 0.002$).

Conclusions GD is an independent risk factor of neonatal SRDS after 34^{0/7} weeks.

Keywords Gestational diabetes · Neonatal severe respiratory distress syndrome · Late preterm and term pregnancy · Maternal obesity

Introduction

Since its original description by O’Sullivan in 1961, the incidence of gestational diabetes (GD) has increased dramatically worldwide [1]. Evolution of alimentary habits, increase of obesity prevalence, and recent diminution of diagnostic threshold values contributed to this increase [2, 3]. The incidence of GD nowadays reaches 17.8% worldwide, becoming a major public health concern [4]. Some materno-foetal complications of GD are now well-identified [5–11]. Thus, GD is known to expose to type 2 diabetes in post-partum [12] and to foetal consequences such as macrosomia, prematurity, and neonatal metabolic disorders such as severe neonatal hypoglycemia, hyperbilirubinemia, and hypocalcemia. Potential long-term and transgenerational effects have also been described [13]. Although an optimal balance of GD has been shown to significantly reduce neonatal morbidity

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and mortality [14], perinatal complications remain more frequent than in general population [10].

Respiratory distress syndrome occurs in a significant number of late preterm and term neonates and represents a major cause of admission in neonatal units with associated morbidity and mortality [15]. Aetiologies are multiple [16], with the two main causes being transient tachypnoea of the newborn related to abnormal lung fluid absorption and deficiency of surfactant. The risk of respiratory distress syndrome in relation with hyaline membrane disease in neonates from patients with GD has been previously reported [6]. However, the definition of respiratory distress syndrome throughout literature is not a homogeneous and the associated risk remains unclear after 34^{0/7} weeks of gestation (weeks). Although we previously identified GD as an independent risk factor for severe neonatal respiratory distress syndrome (SRDS) after 34^{0/7} weeks in a retrospective study with an aOR 11.55 (95% CI 3.9–33.9, $p < 0.001$) [17] and two others retrospective studies gave contradictory conclusions in late-preterm infants from 34^{0/7} to 36^{6/7} weeks [18, 19], to our knowledge, no prospective study has yet demonstrated the association of SRDS and GD in late preterm and term neonates. The aim of this study is to prospectively assess if neonates delivered after 34^{0/7} weeks from mothers diagnosed with GD are exposed to an increased risk of neonatal SDRS.

Methods

Patients

We conducted a prospective cohort study among women who delivered in our tertiary care-level maternity unit in Marseille between January 1st 2011 and July 31st 2012. Women were recruited at the time of their admission in labour ward. All women with a monofoetal pregnancy in beginning of labour after 34^{0/7} weeks of gestation or planned for a caesarean section and who had been systematically screened for GD, according to our institution guidelines, were eligible to participate to the current study. Pregnant women with multiple pregnancy, existence of a pre-gestational diabetes, absence or poor pregnancy follow-up, uncertain dating of pregnancy, absence of systematic GD screening, and in utero foetal death were not included. The study protocol received approval from the Ethics Committee on Research in Obstetrics and Gynecology (CEROG no. 2010-OBS11-02). Written informed consent was obtained from all participants.

Collected data

Age, previous history, weight gain during pregnancy (kg), body mass index (BMI) at the moment of delivery (kg/m^2), and complications of pregnancy and time of occurrence were recorded for all participants. Maternal obesity was defined as $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$. We also recorded the exact term and mode of delivery (spontaneous vaginal delivery, assisted vaginal delivery, and caesarean section), the foetal gender, the neonatal weight, the Apgar score at 5 min, and any diagnosed foetal malformation. Gestational age calculation was based on foetal biometry of cranio-caudal length at first-trimester systematic ultrasound scan performed between 11^{0/7} and 13^{6/7} weeks. Foetal growth restriction was defined as a neonatal weight lower than the 10th percentile and macrosomia as a neonatal weight over the 90th percentile according to the reference curves from the AUDIPOG study [20, 21]. The prenatal administration of corticosteroid therapy before 34^{0/7} weeks consisting in two intramuscular injections of 12 mg of Betamethasone repeated over 24 h was also systematically recorded.

Systematic screening of gestational diabetes

According to our institution guidelines, screening of diabetes was systematically performed in all patients. Screening was performed using glucose tolerance test between 24^{0/7} and 28^{0/7} weeks independently of the existence of any identified maternal risk factors for GD. Overnight fasting plasma glucose was determined just before the administration of 75 g of glucose. Blood for glucose values was drawn at 1 and 2 h. Diagnose of GD was made if at least one abnormal glucose value(s) was identified: glucose value after an overnight fast $\geq 0.92 \text{ g}/\text{L}$; 1-h post-prandial level $\geq 1.80 \text{ g}/\text{L}$; and 2-h post-prandial level $\geq 1.53 \text{ g}/\text{L}$. In case of GD, the type of therapy (dietetic alone or associated with insulin therapy) and glucose level (6 capillary glycaemia per day) were monitored and documented. After 10 days of monitoring, controlled GD was defined by fast glucose values $< 0.95 \text{ g}/\text{L}$ and post-prandial glucose values $< 1.20 \text{ g}/\text{L}$.

Neonatal outcomes and diagnosis of SRDS

The primary outcome was the diagnostic of neonatal SRDS. As the definition of respiratory distress syndrome is quite heterogenic throughout literature, we chose to precisely define the SRDS using both clinical and radiological criteria. Thus, SRDS was defined by the association of clinical signs of early neonatal respiratory distress occurring within the first 2 h following birth, with consistent radiologic features and oxygen dependence requiring invasive and/or non-invasive mechanical ventilation with a fraction of inspired oxygen (FiO_2) > 0.25 for a minimum of 24 h and admission

to neonatal intensive care unit (NICU). Duration of admission in NICU and of ventilation was systematically recorded.

Number of subjects required and power of the study

On a preliminary review of 300 deliveries from our institution, GD was diagnosed in 10.9% of women and was associated with 34.4% of SDRS in the GD group compared with 5.4% in control group ($p < 0.001$) (unpublished data). Based on these results, the number of subjects required was calculated to detect a four-fold increased risk of SRDS in women with GD to achieve a 95% powered study with a 10% incidence of GD. We thus calculated the sample size to be at least of 429 women.

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 software (SPSS Inc. Chicago, IL). Data were expressed as

mean \pm SE or median (min–max). Groups were compared using the χ^2 or Fisher exact test for categorical characteristics and using the Student t test for continuous ones, as appropriate. A two-sided p value <0.05 was considered as statistically significant.

Results

During the study period, a total of 444 pregnant women were included in the current study. GD was diagnosed in 60 patients (13.5%).

Maternal, obstetrical, and neonatal characteristics according to the diagnosis of gestational diabetes

Patients and neonatal characteristics are summarized in Table 1. The groups were statistically different in maternal age and maternal BMI at the time of delivery ($p < 0.001$).

Table 1 Maternal, obstetrical, and neonatal characteristics according to the diagnosis of maternal gestational diabetes

| | Gestational diabetes ($n = 60$) | No gestational diabetes ($n = 384$) | p |
|--|--------------------------------------|--|--------|
| Maternal characteristics | | | |
| Age (years) median (min–max) | 34 (20–44) | 28 (16–42) | <0.001 |
| Smoking | 6 (10) | 54 (17) | 0.188 |
| Nulliparity | 18 (30) | 149 (39) | 0.191 |
| Obesity* | 35 (66) | 115 (35) | <0.001 |
| Obstetrical characteristics | | | |
| Gestational age at delivery (weeks) mean \pm SD | 39.3 \pm 1.6 | 39.5 \pm 1.4 | 0.31 |
| Preterm birth** | 5 (8) | 20 (5) | 0.361 |
| Corticosteroids therapy before 34 ^{0/7} WG | 7 (12) | 7 (2) | <0.001 |
| Induction of labour | 19 (32) | 75 (19) | 0.03 |
| Mode of delivery | | | |
| Spontaneous vaginal delivery | 33 (55) | 263 (68) | 0.061 |
| Operative vaginal delivery | 5 (8) | 38 (10) | |
| Planned c-section | 13 (22) | 35 (9) | |
| Emergency c-section during labour | 9 (15) | 48 (12) | |
| Neonatal outcomes | | | |
| Neonatal weight mean \pm SD (grammes) | 3635.4 \pm 588.0 | 3344.7 \pm 520.3 | <0.001 |
| Macrosomia*** | 13 (23) | 39 (10) | 0.026 |
| Apgar < 7 at 5 min | 7 (12) | 6 (2) | 0.001 |
| Arterial umbilical pH, mean \pm SD | 7.27 \pm 0.11 | 7.29 \pm 0.08 | 0.06 |
| SRDS | 12 (20) | 20 (5) | <0.001 |
| Length of hospitalization in NICU, median (min–max) (days) | 3 (1–16) | 2 (1–14) | 0.46 |
| Length of mechanical ventilation, median (min–max) (days) | 1 (0.04–15) | 1 (0.02–4) | 0.11 |

All values are expressed as n (%) otherwise specified

SD standard deviation, SRDS severe respiratory distress syndrome

* Body Mass index >30 (kg/m²)

** <37 weeks

*** Macrosomia defined as a neonatal weight ≥ 4000 g

Compared to others, women diagnosed with GD were statistically older (mean age 32.5 years vs. 28.7 years, respectively, $p < 0.001$), and significantly more likely to be obese at the moment of delivery (66% vs. 35%, respectively, $p < 0.001$). Although mean gestational age at delivery was not statistically different between the two groups (39.23 ± 1.61 in women with GD vs. 39.45 ± 1.44 in control group, $p = 0.31$), women with GD were significantly more likely to have undergone induced labour ($p = 0.03$). When considering the different modes of delivery (spontaneous vaginal delivery, vaginal-assisted delivery, or caesarean section), no statistical difference was observed between the two groups.

Neonates delivered from women diagnosed with GD presented higher neonatal weight ($p = 0.001$) and higher rate of macrosomia ($p = 0.02$). A neonatal SRDS was diagnosed in 32 cases (7.2%). No statistical difference was found in the median length of admission in NICU of neonates diagnosed with SRDS and in the median duration of mechanical ventilation. No case of neonatal death was recorded. Compared to others, neonatal SRDS was significantly more often observed in neonates from women diagnosed with GD

12 (20%) vs. 20 (5.2%), respectively ($p < 0.001$). A higher proportion of neonates with an Apgar score <7 at 5 min was observed in neonates from women diagnosed with GD ($p = 0.001$), but no statistical difference was found in the mean arterial umbilical pH ($p = 0.06$).

Maternal, obstetrical, and neonatal characteristics according to the occurrence of SRDS

Maternal, obstetrical, and neonatal characteristics according to the occurrence of SRDS are summarized in Table 2. We found no statistical difference between the two groups regarding the following maternal characteristics: age, smoking status, nulliparity, and gestational age at delivery. GD was more frequently observed in women, whose neonates were diagnosed with SRDS 12 (38%) vs. 48 (12%), respectively ($p < 0.001$). Our study failed to identify any statistical difference in case of controlled GD 7 (58.3%) vs. 35 (72.9%), respectively ($p = 0.481$). Women whose neonates presented SRDS were more often obese: 18 (56%) vs. 132 (32%), respectively ($p = 0.002$). Furthermore, women whose neonates were diagnosed with SRDS were significantly more

Table 2 Maternal, obstetrical, and neonatal characteristics according to the occurrence of severe respiratory distress syndrome

| | Neonatal SRDS | | <i>p</i> |
|---|----------------------|----------------------|----------|
| | Yes (<i>n</i> = 32) | No (<i>n</i> = 412) | |
| Maternal characteristics | | | |
| Age median (min–max) (years) | 30.5 (18–40) | 29 (16–44) | 0.882 |
| Smoking | 6 (19) | 64 (16) | 0.631 |
| Nulliparity | 17 (53) | 150 (36) | 0.060 |
| Obesity* | 18 (56) | 132 (32) | 0.002 |
| Gestational diabetes | 12 (38) | 48 (12) | <.001 |
| Obstetrical characteristics | | | |
| Gestational age at delivery mean \pm SD (weeks) | 38.9 ± 2.1 | 39.1 ± 1.5 | 0.394 |
| Preterm birth** | 3 (9) | 22 (5) | 0.411 |
| Maternal corticosteroids therapy before 34 weeks | 4 (12) | 10 (2) | 0.013 |
| Induction of labour | 10 (31) | 83 (20) | 0.049 |
| Mode of delivery <i>n</i> (%) | | | |
| Spontaneous vaginal delivery | 12 (37) | 283 (69) | <.001 |
| Operative vaginal delivery | 7 (22) | 37 (9) | |
| Planned c-section | 2 (6) | 34 (8) | |
| Emergency c-section during labour | 11 (34) | 58 (14) | |
| Neonatal outcomes | | | |
| Neonatal weight, mean \pm SD (grammes) | 3465 ± 696 | 3375 ± 523 | 0.378 |
| Macrosomia*** | 4 (13) | 48 (12) | 0.820 |
| Apgar <7 at 5 min | 8 (25) | 5 (1) | <.001 |
| Arterial umbilical pH, mean \pm SD | 7.21 ± 0.13 | 7.29 ± 0.08 | <.001 |

All values are expressed as *n* (%) otherwise specified

SD standard deviation, SRDS severe respiratory distress syndrome

* Body mass index >30 kg/m²

** <37 weeks

*** Macrosomia defined as a neonatal weight ≥ 4000 g

likely to have received corticosteroids therapy before 34^{0/7} weeks 4 (12.5%) vs. 10 (2.4%), respectively ($p = 0.013$).

Mode of delivery and SRDS

Compared to others, neonates diagnosed with SRDS were significantly more often born by caesarean section: 92 (22%) vs. 13 (40%), respectively ($p < 0.001$). Caesarean sections were performed before 39^{0/7} weeks in 6 cases (46%) in SRDS group versus in 19 (21%) ($p = 0.07$). Furthermore, neonates diagnosed with SRDS were significantly more often born after assisted vaginal delivery: 37 (9%) vs. 7 (22%), respectively ($p < 0.001$).

Identification of independent risk factors for SRDS

In multivariate analysis (Table 3), GD was identified as an independent risk factor of neonatal SRDS (aOR 3.6; 95% CI 1.5–8.6; $p = 0.005$). Other identified risk factors were obesity at time of delivery (aOR 2.8; 95% CI 1.1–7.1; $p = 0.029$) and assisted vaginal delivery (aOR 5.5; CI 95% 1.9–15.9; $p = 0.002$). Foetal macrosomia was not identified as an independent risk factor of neonatal SRDS.

Discussion

To our knowledge, this study is the first prospective study to report GD as an independent risk factor of neonatal SRDS after 34^{0/7} weeks of gestation. We believe these results to be of genuine importance in daily obstetrical practice as it might help for optimal neonatal care in anticipating the need for potential urgent neonatal management.

With a global rate up to 7% of SRDS after 34^{0/7} weeks of gestation, our results are consistent with those of the previous studies [22, 23]. Although using a rigorous definition of SRDS combining clinical and radiological criteria, the

prevalence of SRDS reached up to 20% of neonates from patients diagnosed with GD. It is noticeable that, differently from the previous studies, we did not observe any statistical association between the diagnosis of foetal macrosomia and the occurrence of SRDS [24–26]. Because macrosomia is known as a major complications of GD and controlled GD was demonstrated to be associated with a diminution of the incidence of macrosomia [27, 28], we can hypothesize our results to be explained by the small size of our study. Furthermore, we identified operative vaginal delivery as an independent risk factor of SRDS. We believe this result to be easily explained by the fact that more than the half of operative vaginal deliveries was indicated by non-reassuring foetal heart rate, being the genuine cause of poor neonatal outcome. Caesarean delivery even planned or during labour was not associated with SDRS in multivariate logistic regression contrary to results reported in a recent retrospective study of late-preterm births [19] and lack of power or different period of inclusion (late preterm and term) can explain this difference.

The direct effect of maternal GD on the risk of neonatal SRDS may have physiopathological and clinical explanations. First, GD has been experimentally shown to induce both insufficient and an abnormal maturation of surfactant due to immaturity of type II alveolar cells from rats, with particularly important effects at the end of pregnancy [29]. Furthermore, phosphatidyl glycerol, an essential component of surfactant, may be diminished, due to a delayed secretion in case of unbalanced GD [30]. Second, induced labour or planned caesarean section is more likely to be performed in cases of GD, independently of suspected macrosomia, resulting in an increased risk of neonatal respiratory distress syndrome due to a delayed resorption of pulmonary liquid or “wet lung” [31–33]. Our study reported that women diagnosed with GD were more likely to have undergone induced labour and neonates diagnosed with SRDS were more often born after the induction of labour. Finally, GD is known to be associated with an increased risk of prematurity. A prospective cohort study on 46,230 pregnancies reported this risk to depend on the levels of maternal glycemia, independently of perinatal complications that could have triggered early delivery such as gestational hypertension, pre-eclampsia, hydramnios, or macrosomia [34]. Another study comforted these results in women with impaired glucose tolerance [35]. We found in our study a trend of increasing risk of preterm birth in women with GD but our study failed to demonstrate a significant difference, possibly because of a lack of power, with small effectives in each group.

We found obesity to be an independent risk factor of SRDS. This finding is consistent with the previous literature as maternal obesity has already been shown to be associated with a significantly higher risk of perinatal death [36]. Obesity in women with GD has also been documented to

Table 3 Identification of factor having a significant and independent impact on the risk of severe neonatal respiratory distress syndrome in multivariate logistic regression

| | AOR | 95% CI | <i>p</i> |
|-----------------------------------|-----|----------|----------|
| Obesity* | 2.8 | 1.1–7.1 | 0.029 |
| Gestational diabetes | 3.6 | 1.5–8.6 | 0.005 |
| Planned c-section | 1.9 | 0.6–6.0 | 0.284 |
| Emergency c-section during labour | 2.9 | 0.9–9.2 | 0.071 |
| Operative vaginal delivery | 5.5 | 1.9–15.9 | 0.002 |
| Macrosomia** | 0.9 | 0.3–2.9 | 0.848 |

CI confidence interval, AOR adjusted odds ratio

* BMI > 30 (kg/m²)

** Defined as a neonatal weight ≥4000 g

be associated with a higher proportion of adverse neonatal outcomes, including the need respiratory support [37]. Our study failed to identify a benefit in the achievement of optimal glycaemic level during pregnancy. Such optimal balance of glucose level by insulin therapy has, however, been previously shown to be the sole factor associated with a reduction of neonatal complications in women with GD [14, 38]. Although early optimal balance of GD seems to be crucial to reduce neonatal complications, the association of controlled GD and of decreasing risk of SRDS remains undemonstrated. However, the small effectives in each group and a non-dedicated design of our study do not allow for any genuine conclusion and further large prospective studies remain needed to properly answer to that question.

Our results raise concerns regarding the potential benefit of corticosteroids therapy performed between 34^{0/7} and 36^{6/7} weeks in case of GD with the risk of imminent delivery to reduce the risk of SRDS. This question was asked in a retrospective study with a higher proportion of infants from the GD group receiving corticosteroids but without impact on logistic regression analysis [18]. A randomized trial recently suggested that the administration of betamethasone to women at risk for late-preterm delivery (from 34^{0/7} to 36^{5/7} weeks) could significantly reduce the rate of neonatal respiratory related morbidity [39]. In this trial, the proportion of women with GD was the same in both betamethasone and placebo groups (around 10%). It is, however, noticeable that the primary outcome was a neonatal composite of treatment in the first 72 h and did not specifically describe the severity of SRDS. Although that outcome decreased from 14.4% (placebo) to 11.6% (betamethasone), the incidence of neonatal hypoglycaemia was greatly increased in the steroid group. At this stage, the benefit of corticosteroids therapy in patients with GD and threatened late-preterm delivery remains, however, questionable; more studies are needed to investigate this point.

Finally, in showing GD to be an independent risk factor of neonatal SRDS after 34^{0/7} weeks of gestation, our results suggest the need of reorganizing the management of pregnant women diagnosed with GD and to decide, where these patients should deliver, especially since the incidence of GD reaches 13.5% in our study. This incidence is lower than reported in the French national perinatal surveys in 2010 (7.2%) in general population but concordant with incidence in high risk population in France (10–20%) [40]. However, this incidence is lower than the worldwide incidence probably because of difference in incidence of obesity, maternal age, ethnicity, and other factors influencing the occurrence of GD. As recently highlighted by the European Consensus Guidelines on the Management of Respiratory Distress Syndrome [41], “optimizing the outcome for babies with respiratory distress syndrome includes good obstetric practice and consideration of whether transfer to a perinatal centre

is necessary and safe”. Nowadays, GD still does not justify management in a specific level of care maternity unit. Most will deliver in low level of care maternity units, with paediatrician not being systematically present at the time of delivery. Our results bring additional arguments for a genuine reflection about these recommendations.

Conclusion

GD is an independent risk factor of neonatal SRDS after 34^{0/7} weeks. This risk is also increased in obese women. These results confirm the need for careful GD screening during pregnancy, with antenatal prevention of maternal obesity. They also suggest the need for anticipation of the management of pregnant women diagnosed with GD and specially to transfer them in perinatal centre with the possibility of systematic immediate neonatal paediatric management if required.

Author contributions MI: data collection and manuscript writing, BJ: manuscript writing, TB: reviewing, GC: supervision and methodology, BF: supervision and methodology, CX: Project development, reviewing, and supervision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the national research committee and the study protocol received approval from the Ethics Committee on Research in Obstetrics and Gynecology (CEROG no. 2010-OBS11-02).

Informed consent Written informed consent was obtained from all participants included in the study.

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