Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications

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Abstract

Objective: To evaluate the risks of perinatal complications in infants born to mothers with treated or untreated gestational diabetes mellitus (GDM).

Methods: A search of the PubMed database was performed and recommendations from NICE and the French National Authority for Health were consulted.

Results: Untreated moderate or severe GDM increases the risk of foetal and neonatal complications (EL1). The risk of malformations slightly increases in newborns of mothers with GDM compared to the general population (EL2). This risk is probably associated with the presence of undiagnosed type 2 diabetes among patients with GDM (EL2). There is a linear relationship between maternal blood glucose levels and an increased birth weight (EL2). Treatment for GDM reduces the incidence of macrosomia (EL1). Although the risk of cardiomyopathy in cases of GDM cannot be accurately estimated based on the available data, severe clinical forms are rare. The risks of neonatal asphyxia and perinatal mortality are no higher in infants born to women with GDM (EL2). Birth injuries and brachial plexus injuries are rare, and no more likely to occur in cases of untreated GDM. It is difficult to assess the risk of respiratory distress, regardless of its cause. It is not possible to establish a link between GDM and neonatal respiratory problems due to insufficient data. Although the risk of neonatal hypoglycaemia is difficult to determine due to the variable definitions reported in the literature, the incidence of hypoglycaemia requiring intravenous therapy is low (EL1). The risks of hypocalcaemia (EL4) and hyperbilirubinemia (EL1) are similar to the general population.

Conclusion: Serious perinatal complications specifically associated with GDM are rare. Macrosomia has been demonstrated to be the predominant adverse outcome in cases of GDM. It is the main factor linked to reported cases of complications in GDM. Maternal obesity is an additional risk factor for complications, regardless of diabetes status.

Keywords: malformations, macrosomia, excessive foetal growth, hypoglycaemia, perinatal asphyxia, birth injuries, gestational diabetes mellitus, complications, review

Résumé

Complications fœtales et néonatales du diagnostic gestationnel : mortalité péritalale, malformations congénitales, macrosomie, dystocie des épaules, traumatisme obstétrical, complications néonatales

Objectif : Évaluer les risques de complications péritalales en cas de diabète gestationnel (DG) traité ou non.

Méthodes : Recherche bibliographique effectuée par consultation des banques de données Pubmed et les recommandations HAS et NICE.

Résultats : Le DG modéré ou sévère non traité augmente le risque de complications fœtales et néonatales (NP1). Le risque de malformations est modérément augmenté en cas de DG par rapport à la population générale (NP2). L’augmentation du risque de malformations est probablement liée à l’existence de cas de diabète de type 2 méconnus parmi les patientes avec DG (NP2). Il existe une relation linéaire entre le niveau de la glycémie maternelle et l’augmentation du poids de naissance (NP2). Le traitement du DG diminue l’incidence de la macrosomie (NP1). Les données de la littérature ne
permitting that the risk of cardiomyopathy in case of DG, but the forms severe are exceptional. The risk of asphyxia neonatal and of deaths perinatal n’est pas augmenté dans le cadre du DG (NP2). Les traumatisms obstétricaux and the atteintes du plexus brachial sont des événements rares and l’augmentation of the risk in case of DG non traité n’est pas démontrée. Le risque de détresse respiratoire toutes causes confondues est difficile à apprécier. Il n’existe pas assez de données pour établir un lien entre le DG et les troubles respiratoires néonataux. Le risque d’hypoglycémie néonatale est difficile à apprécier en raison of the hétérogénéité of the définition of the hypoglycémie dans les différentes études, mais the fréquence of the hypoglycémie nécessitant un traitement par voie intraveineuse est faible (NP1). The risque d’hypocalcémie (NP4) and d’hyperbilirubinémie (NP1) is analogue to celui of the population générale.

Conclusion : Les complications périnatales graves liées spécifiquement au DG sont rares. La macrosomie est la principale conséquence néonatale démontrée d’un DG. Elle est le facteur essentiel lié aux complications rapportées en cas de DG. L’obésité maternelle est un facteur de risque de complications surajouté et indépendant du diabète.

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Mots-clés : malformations, macrosomie, excès de croissance foetale, hypoglycémie, asphyxie périnatale, traumatisms obstétricaux, revue

1. Materials and methods

The bibliographic search was performed using PubMed by prioritising the studies published during the last ten years (January 2000 to April 2010). The following search terms were used: gestational diabetes and pregnancy outcomes/untreated gestational diabetes/gestational diabetes and malformations/ gestational diabetes and birth defects/ gestational diabetes and macrosomia/ gestational diabetes and foetal growth/ gesta

The references from the chosen articles and from several review articles were analysed in a search for additional relevant studies. Recommendations from the following learned societies were consulted: French National Authority for Health (Haute Autorité de santé: HAS) www.has-sante.fr/publications; National Institute for Health and Clinical Excellence (NICE) www.nice.org.uk. The references that were not found in the previous search were selected.

Only articles written in English or French were kept. The articles were classified by level of evidence as follows: meta-analyses, randomised controlled trials (RCT), non-randomised controlled trials, cohort studies. For any given chapter, the articles with the highest level of evidence were selected and discussed first.

When a given question could not be answered based on the references selected from 2000-2010, the most recent pre-2000 articles with the highest level of evidence were kept.

2. Introduction

The first studies on gestational diabetes mellitus (GDM), among others, demonstrated an increase in perinatal mortality [1-3].

A number of studies have proven that high maternal blood glucose is associated with macrosomia, foetal morbidity and subsequent complications in the neonatal period [4]. Many of these studies were of type 1 or type 2 diabetes. The incidence and the severity of foetal and neonatal complications in cases of GDM appear to be different to those reported for type 1 or type 2 diabetes.

A recent systemic review and meta-analysis evaluated the effects of treatment in women with GDM [5]. This study analysed five RCTs comparing specific treatment with usual care, and 13 RCTs comparing specific treatments of varying intensities. The authors concluded that treatment for GDM lowers the risk of some neonatal complications (EL1).

The discussion in this chapter will also be based on two recent cohort studies which reported an increased incidence of certain neonatal complications in infants born to women with untreated GDM [6, 7].

3. Gestational diabetes and malformations

Poor maternal glycaemic control in the periconceptual period increases the risk of malformations. This risk is particularly recognised in pregnant women with pre-existing diabetes. However, an increased risk of malformations has been associated with GDM in several patient registry studies, as well as prospective and retrospective cohort studies. According to a review of the studies published between 1990 and 2005 analysing teratogenicity associated with diabetes, there is an increased risk of congenital
malformations in cases of GDM [8] (EL2). The authors determined that this observation was probably related to the inclusion of women with undiagnosed type 2 diabetes in the GDM group.

A study carried out in the state of Washington gathered data on 1,511 births to mothers with pre-existing diabetes and 8,869 births to mothers with GDM, using birth certificate data from all single liveborn infants between 1984 and 1991. The control group consisted of 8,926 singleton infants born to non-diabetic mothers, randomly recruited over the study period, but with the same distribution of year of birth. The risk of malformation was slightly higher in newborns of mothers with GDM, with a prevalence of 2.4% in the non-diabetic group, 2.8% in the GDM group and 7.2% in the group with pre-existing diabetes. The OR was 4 (3.1-5.1) for pre-existing diabetes and 1.3 (1.0-1.6) for GDM [9] (EL2).

Another study examined 8,688 infants of mothers with GDM based on data from the national registry of births between 1987 and 1997. When the study population was compared to the entire registry population (n = 45214), an OR of 1.06 was reported for all malformations combined. Although the overall rate of malformations was not higher in this group, the study found an increased incidence of specific cardiac malformations, oesophageal atresia and spinal anomalies [10] (EL2).

A case-control study based on the data from the National Birth Defects Prevention Study (NBDPS), which included 13,030 births between 1997 and 2003, found malformations to be less common in cases of GDM compared to cases of pregestational diabetes [11]. Odds ratios between GDM and all isolated and multiple malformations were 1.42 (1.17-1.73) and 1.50 (1.13-2.00) respectively. This association was limited to infants of mothers with a pregestational BMI > 25 kg/m² (EL3).

A cohort study of 4,180 pregnancies complicated by GDM (n = 3,764) or type 2 diabetes (n = 416), evaluated the relationship between different types of congenital malformations and maternal blood glucose concentration at entry into prenatal care [12]. Fasting plasma glucose (FPG) levels were measured at 22.6 WG ± 9.2 and 22.2 WG ± 8.9 (mean values) for minor and major malformations respectively. The malformations identified in women with gestational or type 2 diabetes were the same as those observed in cases of type 1 diabetes: cardiovascular defects and anomalies involving the musculoskeletal and central nervous systems. Further, FPG levels at entry into prenatal care were strongly predictive of congenital malformations: the rate of major malformations was 2.1% when initial FPG was < 1.2 g/L (6.6 mmol/L); 5.9% when FPG was between 1.2 and 2.0 g/L (6.6-11.0 mmol); and 12.9% when FPG exceeded 2 g/L (11 mmol) (p < 0.0001) (EL2).

A cohort study based on the data gathered in a hospital birth registry between 1991 and 2000 evaluated the risk of malformations in infants born to women with GDM compared to pregestational diabetes (type 1 or 2) [13]. In their analysis, the authors considered two types of GDM: women with FPG values < 1.05 g/L (5.8 mmol/L) were treated with diet alone and diagnosed as having Class A1 GDM (classification by White); and women with FPG values > 1.05 g/L were treated with insulin and diagnosed as having Class A2 GDM. The mean FPG value in this group was 1.24 ± 0.23 g/L (6.82 ± 1.2 mmol/L). All women with risk factors underwent immediate screening for diabetes. Routine screening was then performed between 24 and 28 WG for all non-diabetic pregnant women. For women with diabetes, FPG was measured at every follow-up visit. The risk of major malformations was no higher in the A1 GDM group than in the non-diabetic group (OR = 0.8 [0.5-1.2]), but was markedly higher in the A2 GDM group (OR = 3.4 [1.9-6.2]). This study concluded that there are two types of diabetes among women with GDM: (1) diabetes which is strictly related to the pregnancy, for which there is no increased risk of malformations; and (2) diabetes diagnosed during pregnancy, with abnormal blood glucose levels in the periconceptual period, for which the risk of malformations is similar to the risk in pregestational diabetes (EL2).

A cohort study carried out between 1986 and 2002 of 2,060 infants of women with GDM (diagnosed according to WHO criteria) analysed the relationship between congenital malformations and the severity of GDM [14]. The rate of congenital malformations was 6% for minor and 3.8% for major malformations. Logistical regression revealed that the risk of malformations was positively and significantly related to 1hr blood glucose values in diagnostic OGTT, and to maternal pre-pregnancy BMI. Conversely, there was a negative relationship with gestational age at diagnosis; an earlier GDM diagnosis was associated with a higher risk of malformations (EL2).

Therefore, according to the data gathered from the literature, there is an increased risk of malformations when:

- GDM is diagnosed during early pregnancy;
- maternal blood glucose levels are significantly high, particularly FPG values;
- pre-pregnancy maternal BMI is high;
- these situations suggest the presence of undiagnosed pre-pregnancy type 2 diabetes.

• The risk of malformations slightly increases in cases of GDM compared to the general population. This risk is probably associated with the presence of undiagnosed type 2 diabetes among women with GDM (EL2).
• A relationship exists between the risk of malformations, maternal blood glucose levels, gestational age at diagnosis of GDM and maternal obesity, all of which are found in type 2 diabetes (EL2).
• The malformations described in cases of GDM are similar to those reported in pregestational diabetes (cardiovascular, musculoskeletal and CNS defects) (EL2).
4. Effects of hyperinsulinism on foetal growth: macrosomia and hypertrophic cardiomyopathy

4.1. Definition of macrosomia

In the literature, a distinction is made between the terms “macrosomia” and “large for gestational age” (LGA).

Macrosomia is defined by an upper birth weight threshold somewhere between 4,000 and 4,500 g, depending on the study. However, in this definition, gestational age is not taken into account.

According to various studies, the term LGA corresponds to a birth weight ≥ 90th percentile or > +2SD (> 97th percentile) for gestational age. This more precise definition takes gestational age at birth into consideration and allows premature newborns with excessive foetal growth to be identified. However, a large number of data curves are used to evaluate newborn growth, and they are based on anthropometric data taken from different populations. As a result, the threshold weight values for defining a LGA newborn differ between the various available curves. Most published studies do not specify which curve they used.

Both terms, macrosomia and LGA, refer to a clinical observation, but do not systematically define a pathological condition. Among macroms or LGA newborns, there is a high proportion of infants who achieve their genetic potential for growth. They are referred to under the term “constitutional” or “symmetric” macrosomia. The growth of these newborns is in proportion to their weight, height and head circumference, and is not associated with other anomalies [15]. Macrosomia in newborns of diabetic mothers is characterised by excess body fat, an increase in muscle mass and organomegaly without increased brain size.

In a single-centre retrospective study analysing all newborns with a birth weight > 4,000 g over a 3 year period (2003-2005), only 41/303 infants (13.5%) had diabetic mothers and 262/303 (86.5%) had non-diabetic mothers [16]. However, the type of diabetes and the exact strategies used for diabetic screening during pregnancy (targeted or not, term of pregnancy), were not given.

Throughout the rest of this chapter and in chapter “Management of infants born to mothers with gestational diabetes”, macrosomia is used as a non-specific term to refer to both LGA newborns, and infants born with a birth weight above 4,000 g.

4.2. Physiology and risk factors associated with macrosomia and organomegaly in gestational diabetes mellitus

According to Pederson, macrosomia in infants of diabetic mothers is the result of foetal hyperinsulinism secondary to maternal hyperglycaemia [17]. Insulin is the main growth factor for foetal growth. The trophic effect of insulin is the result of several mechanisms: insulin stimulates the intake and use of nutrients by insulin-sensitive tissues (adipose tissue); it has a direct mitogenic effect; and it interacts with the insulin-like growth factor (IGF) system by stimulating the production of IGF-1.

Older studies have shown increased cord C-peptide levels in newborns of diabetic mothers. In 1979, Sosenko et al. demonstrated that C-peptide levels were correlated with the severity of maternal diabetes, macrosomia and the risk of hypoglycaemia [18] (EL3).

A very recent prospective study, HAPO, which included more than 23,000 untreated patients, found a continuous association between increased maternal glycaemia (fasting, and at 1 and 2 hours after 75 g test) and foetal hyperinsulinism, evaluated by cord C-peptide levels and birth weight > 90th percentile [19] (EL2).

Based on the data from the HAPO study on 19,885 newborns, an analysis was performed of the link between maternal glycaemia, neonatal body composition and foetal hyperinsulinism. The results show that there is a linear and continuous relationship between percentage body fat in newborns (evaluated by anthropometric and skin fold measurements), maternal glycaemia (fasting, and at 1 and 2 hours after 75 g test), and foetal insulin levels estimated by measurement of cord C-peptide levels [20]. This means that maternal glycaemia values below those defining GDM may be associated with excessive foetal growth, particularly in relation to adipose tissue (EL2).

A prospective cohort study included 668 women who were non-diabetic when screened at 28 WG by 75 g test (FPG < 1.1 g/L [6.1 mmol/L] and 2 hr glucose ≤ 1.55 g/L [8.6 mmol/L]). The risk of macrosomia (weight > 90th percentile for gestational age and sex) was independently associated with fasting maternal blood glucose (OR = 2.61 [1.15-5.93] for +0.18 g/L or 1 mmol/L) and pregestational maternal BMI (OR = 1.1 [1.04-1.18] for +1 kg/m²). Maternal glycaemia and newborn skin fold measurements (that evaluate body fat) were found to be positively correlated (P<0.0001) [21] (EL2).

In the study by Ostlund et al., 213 women with untreated glucose intolerance (GI) were prospectively included from 1997-2001 [7]. GI was defined by FPG < 1.2 g/L (6.7 mmol/L) and 2 hr blood glucose after 75 g OGTT between 1.6 and 2.0 g/L (9 and 11.0 mmol/L). For every woman included with GI, four control subjects were recruited in the same centre (n = 812). In the GI group, there was a significantly higher rate of macrosomia (33% versus 16.4% for a birth weight > 4,000 g and 4.3% versus 0.2% for a birth weight ≥ 5,000 g [P < 0.0001]), and of newborns with a birth weight > +2SD for gestational age and sex (24.9% versus 4.2%, P < 0.0001). Excess foetal growth was associated with GI during pregnancy (OR = 7.3 [4.1-12.7]) after adjustment for BMI, parity, hypertension, pre-eclampsia and ethnicity. It should be noted that maternal obesity (BMI ≥ 30 kg/m²) was also associated with macrosomia after adjustment (OR = 5.0 [2.5-10.0]) (EL3).

There are other risk factors contributing to excessive foetal growth that are often associated with gestational
diabetes, and therefore act as confounding variables. These are maternal BMI during early pregnancy [22, 23] (EL2), excessive weight gain during pregnancy [24] (EL2), maternal age > 40 years and parity > 4 [25] (EL2).

4.3. Effects of GDM treatment on macrosomia

A review by Horvath et al., which included five RCTs comparing treatment groups with groups receiving routine care, found the rates of macrosomia and excessive foetal growth to be significantly lower following specific GDM treatment. The meta-analysis for these two parameters identified ORs of 0.38 (0.30-0.49) and 0.48 (0.38-0.62) respectively [5] (EL1).

Langer et al. carried out a retrospective case-control study between January 1990 and September 1999 including 555 women with untreated GDM (diagnosed after 37 WG), 1,110 women with treated GDM (two steps screening 50 and 100 g OGTT according to the Carpenter-Coustan criteria), and 1,110 non-diabetic women [6]. Each woman with untreated GDM was matched with two women with treated diabetes and two non-diabetic women (control) on the following criteria: obesity; parity; ethnicity; gestational age at delivery; and year of birth. The risk of macrosomia (weight > 4,000 g) was significantly higher in the untreated GDM group compared to the control group, but not in the treated GDM group compared to the control group. OR for untreated GDM versus control was 2.66 (1.93-3.67), and OR for treated GDM versus control was 1.13 (0.82-1.55). The results were similar for the analysis of LGA (weight > 90th percentile). OR for untreated GDM versus control was 3.28 (2.53-3.67), and OR for treated GDM versus control was 1.06 (0.81-1.38). No risk comparisons were made between the treated and untreated GDM groups. Based on maternal BMI stratification, there was a higher rate of macrosomia in the untreated obese/overweight subgroup (BMI > 25 kg/m²) compared to the untreated group with normal body weight (BMI between 21 and 24.9 kg/m²) (40% versus 16%, P < 0.01). There was no increase in the rate of macrosomia for obese/overweight women with treated diabetes, compared to non-diabetic women or women with treated diabetes and normal body weight (EL4).

4.4. Cardiomegaly

Myocardial hypertrophy is classically described in foetuses or newborns of diabetic mothers. It is characterised by an increase in the number and size of myocardial cells and is associated with myofibrillar hypertrophy and hyperplasia, without myocardial fibre disarray [26]. This leads to hypertrophy of the ventricular walls, usually predominantly involving the septum. The physiopathological mechanisms at the origin of cardiomyopathy are unknown, and there is no evidence on this subject in the literature.

Myocardial hypertrophy is associated with an overall decrease in ventricular compliance and an increased contractility of the left and right ventricles. Major septal hypertrophy can lead to subaortic stenosis and secondary mitral insufficiency.

Current knowledge is based on ECG ultrasound data carried out antenatally and postnatally or on post-mortem data.

In one of the largest prenatal studies, Veille et al. found septal hypertrophy in 75% of the 64 foetuses of diabetic mothers, and a correlation between maternal HbA1c levels and septal size [27]. In this study, 35/62 women had GDM controlled by diet only and 39/64 had type 1 diabetes. These two groups were not separated in the results analysis (EL4).

Oberhoffer et al. reported on a group of 104 infants born to 100 diabetic mothers (41 cases of GDM and 59 cases of type 1 diabetes), among which 25% had myocardial hypertrophy predominantly affecting the septum. There was no relationship between the type of diabetes and quality of maternal diabetic control, the cord insulin or C-peptide, and the presence of myocardial hypertrophy [28] (EL4).

The data gathered between 1980 and 2003 from an anatomopathological analysis of stillborn infants (cause unknown) of diabetic mothers have recently been reported. Twenty-one foetuses from mothers with diabetes were studied: 11 had a weight > 90th percentile, 10 had a normal weight. Cardiomegaly (i.e. heart weight > +2SD for gestational age) was reported in 7 foetuses. Three of these came from mothers with GDM, and four from mothers with type 1 diabetes. After adjustment for body weight, stillborn infants of mothers with diabetes (all types) had heavier hearts and thicker ventricular walls compared to eutrophic or macrosomic (weight > 10th percentile) stillborn infants born to non-diabetic mothers. Hypertrophy was not confined to the septum; it also affected the left ventricular free wall. Cardiomyopathy was considered to be a possible cause of stillbirth due to heart failure [26] (EL4).

A retrospective, single-centre study evaluated the risk of myocardial hypertrophy according to the type of diabetes, using data gathered over two years from 2003 to 2005. There was only one (2%) case of ventricular hypertrophy among 54 GDM pregnancies, versus 7/16 (41%) cases from type 1 diabetes and 4/22 (22%) from type 2 diabetes. The conditions of GDM diagnosis were not specified and no comparison was made with the general population [29] (EL4).
There are currently no studies that enable a strong link to be established between GDM, isolated septal hypertrophy and foetal risk. This point is discussed in detail in chapter “Prenatal obstetric monitoring”, which describes the strategies for screening and monitoring cardiomyopathy in the prenatal period.

- Although foetal cardiomyopathy is a well-recognised complication of diabetes during pregnancy, there is a poor level of supporting evidence in the literature (NP4).
- It is not possible to estimate the rate and exact risk of cardiomyopathy in cases of GDM, or to evaluate the link with maternal glycaemia based on the data available in the literature. Severe forms are rare in infants born to mothers with GDM.

5. Foetal and neonatal asphyxia, perinatal death

According to several prospective and retrospective studies involving type 1 diabetes pregnancies, the factors that reflect foetal asphyxia are an increased incidence of foetal cardiac rhythm disturbances, cord blood acidosis and a low Apgar score [30-32]. These events are related to chronic foetal hypoxia, which causes an increase in foetal erythropoiesis and secondary polyclonuglobula [32-34]. Foetal asphyxia theoretically increases the risk of perinatal asphyxia and death.

A prospective study including 37 newborns of mothers with treated GDM and 38 control subjects evaluated foetal hypoxia and acidosis on umbilical cord blood [35]. All births were caesareans indicated by previous caesarean, breech or abnormal presentation, or for maternal reasons that did not affect foetal growth. A 100 g OGTT was performed between 28 and 32 WG to screen for diabetes, which was defined by at least two values above 0.95 g/L (5.2 mmol/L) for fasting glucose, 1.8 g/L (10 mmol/L) at 1 hr, 1.55 g/L (8.6 mmol/L) at 2 hrs, and 1.4 g/L (7.7 mmol/L) at 3 hrs. The newborns of mothers with GDM were more hypoxic (O2 saturation: N 63.2 ± 13.9%; GDM 53.8 ± 14.6%, P < 0.01; O2 content N 5.5 ± 1.4; GDM 4.8 ± 1.2 mmol/L, P < 0.05) and had higher lactate concentrations (N 1.32 ± 0.49; GDM 1.64 ± 0.75 mmol/L, P < 0.05). Seven of the newborns of mothers with GDM had a weight > 4,000 g, two were large for gestational age (weight > 90th percentile) and two were small for gestational age (weight < 10th percentile). A normal Apgar score was recorded for all newborns (EL3).

Although the exact pathogenesis of foetal asphyxia is unknown, several causes for insufficient foetal oxygen supply have been suggested. Foetal hyperglycaemia and hyperinsulinism lead to an increase in oxygen consumption combined with a decrease in oxygen content in the umbilical artery, as demonstrated in foetal lambs [36]. One study found that maternal HbA1c during the last month of pregnancy correlated with foetal erythropoiesis, reflecting the link between maternal glycaemia control and foetal hypoxaemia [37]. One of the invoked mechanisms is augmented foetal anabolism, which increases oxygen demand and leads to relative hypoxia. Placental anomalies have been described during GDM, even when diabetes is stable during pregnancy. Placenta size increases with a lower foetal/placental weight ratio. Degenerative lesions (fibrinoid necrosis and vascular lesions) and villous immaturity are present, and there is an increase in nucleated foetal red blood cells, indicating chronic foetal hypoxia [38].

Unlike in pregestational diabetes, the increased rate of foetal deaths in the 2nd and 3rd trimesters of pregnancy is debatable in cases of GDM [39, 40].

A literature analysis including studies comparing diet- or insulin-treated diabetes with routine care, or the effectiveness of specific treatments, revealed no significant difference between the two groups in terms of neonatal or perinatal mortality [5] (EL1). The ACHOIS study by Crowther et al., which compared a group of 490 women with moderate untreated GDM (75 g OGTT, fasting glucose < 1.4g/L (7.8 mmol/L) and 2 hr blood glucose between 1.4 and 2 g/L (7.8-11 mmol/L), with a group of 510 women with treated GDM, is the only study to have reported a difference in perinatal mortality: five deaths occurred in the routine-care group, whereas there were none in the treatment group. Two stillbirths were unexplained intrauterine deaths at term, another at 35 WG was associated with pre-eclampsia and growth restriction, and two newborns died; one from a lethal congenital malformation, the other after an asphyxial condition during labour. This difference was not significant (P = 0.07) [41] (EL2).

In the same study, no difference was found between the two groups in the incidence of an Apgar score < 7 at 5 minutes: there were 6 (1%) infants in the treatment group versus 11 (2%) in the routine-care group (P = 0.26) (EL2).

In the study by Langer et al., the risk of a cord pH < 7.2 was no different between the treated GDM, untreated GDM and control groups. The rate of stillbirths was 5.4/1000, 3.6/1000 and 1.8/1000 respectively. The OR was not significant between untreated diabetic and control subjects (OR = 1.91 [0.27-14.08]), or between the treated diabetic and control subjects (OR = 2.00 [0.18-22.10]) [6] (EL2).

In a respective cohort study which included more than 83,000 births over a period of 12 years, perinatal mortality was evaluated for groups of non-diabetic mothers (n = 82,025), mothers with type 1 diabetes (n = 160), mothers with type 2 diabetes diagnosed before pregnancy (n = 256), and mothers with GDM (n = 1,110). In the GDM group, 178 (16%) mothers were diagnosed with type 2 diabetes six weeks after delivery. When these mothers were excluded from the GDM group, perinatal mortality was 8.9/1000, which was similar to the general population (12.5/1000). Perinatal mortality in the group with type 2 diabetes diagnosed before pregnancy was 39.1/1000. Mortality was the highest in the group with type 2 diabetes diagnosed after pregnancy, with 56.2/1000 perinatal deaths. In both groups of women with type 2 diabetes, BMI
was higher than in the type 1 diabetes group (33.9 and 34.9 versus 25.2 kg/m² respectively) [42] (NP2).

Among the 23,316 women included in the HAPO study, 130 perinatal deaths were recorded. Although this study did not have the statistical power to examine this parameter as a primary outcome, no increase was found in the risk of perinatal death with increasing maternal glucose levels [19] (EL2).

Other studies have shown that maternal obesity is a risk factor for perinatal death.

A meta-analysis including five cohort studies published between 2001 and 2005, and three case-control studies published between 1993 and 2001, showed that the risk of mortinatality was twice as high in cases of pregestational maternal obesity (BMI > 30 kg/m²) (OR = 2.04 [1.30-3.17]). This study did not enable risk factors associated with obesity and linked to mortinatality to be determined [43] (EL2).

In a retrospective cohort study which included 26,424 pregnant women, the authors analysed pregnancy outcomes according to maternal BMI. There was an increased risk of foetal death (defined by term < 22 WG or weight < 500 g) or perinatal death (> 22 WG or weight > 500 g or during 1st week of life) in overweight and obese women. Among these women, the risk of foetal or perinatal death was doubled (OR = 2.35 [1.28-4.32] and OR = 2.19 [1.33-3.62] respectively) [44] (EL2).

In a retrospective cohort study of 167,750 women, the authors analysed the risks of late foetal death (> 28 WG) and early neonatal (1st week of life) deaths, according to pre-pregnancy maternal BMI [45]. The risks of late foetal death and neonatal death increased with maternal BMI, especially for overweight, nulliparous women (BMI > 25.0-29.9) and obese women (BMI > 30 kg/m²) (EL2).

Macrosomia, regardless of the cause, is in itself a risk factor for asphyxia and perinatal death. In a retrospective study of around 6 million births, the risk of an Apgar score < 4 at 5 minutes was doubled when birth weight was between 4,500 and 4,999 g, and increased six-fold when birth weight was > 5,000 g [46]. There was an increase in early neonatal deaths, with an OR of 1.8 (1.3-2.4) for a birth weight between 4,500 and 4,999 g, and an OR of 6.4 (3.9-10.4) for a birth weight over 5,000 g. The rate of diabetes, regardless of the type, for each of these birth weight groups was 5.4 and 11.5% respectively (EL2).

- The increased risk of perinatal death associated with GDM seems to be attributable to undiagnosed type 2 diabetes (NP2).
- Maternal obesity is often associated with type 2 diabetes or gestational diabetes and is a risk factor for perinatal death (NP2).
- The risk of asphyxia and perinatal death is increased in infants with severe macrosomia (weight > 4,500 g), especially if weight is > 5,000 g, regardless of the cause of macrosomia (NP2).

6. Birth injuries: shoulder dystocia, fractures and brachial plexus injuries

Birth injuries are usually attributed to macrosomia, which increases the risk of shoulder dystocia, regardless of the cause of excessive growth. In the study by Zhang et al., the risk of birth injury was higher for infants with a birth weight between 4,500 and 4,999 g, and > 5,000 g, with an OR of 2.4 (2.2-2.5) and 3.5 (3.0-4.2) respectively [46] (NP2).

In the study by Langer et al., the rate of shoulder dystocia in the three groups (untreated GDM, treated GDM, control) was 1.6%, 1.2% and 0.4% respectively in women with normal body weight, and 3.2%, 0.7% and 0.8% in overweight or obese women. The differences were not significant, but the results lacked statistical power [6].

The different studies of GDM have shown a significant decrease in the risk of dystocia when diabetes is treated or treatment is intensified [5] (EL1). However, dystocia is only considered to be a serious event if it is accompanied by a birth injury. A meta-analysis of the two randomised studies comparing specific treatment with routine care [41, 47] found a non significant decrease in birth injuries in the treatment group (OR = 0.39 [0.13-1.15], P = 0, 088) [5] (NP1).

In the study by Osland et al., the rate of brachial plexus palsy was 1.9% in newborns of mothers with GI, versus 0.1% in the control group (P = 0.007). However, this event was very rare (4/421 patients versus 1/810 patients respectively), which meant that the risk could not be accurately measured [7].

Brachial plexus palsy in newborns of diabetic mothers is rare; the incidence rate has been reported to be between 2.0 and 3% [48]. In a retrospective cohort study of 36,241 singleton pregnancies, the authors compared the perinatal outcome according to whether GDM was present, and whether birth weight was < 4,000 g or ≥ 4,000 g [49]. GDM was tested by 50 g followed by 100 g OGTT between 24 and 28 WG in women without risk factors. For women considered at high risk, screening during the 1st trimester was performed; if screened negative, they then underwent repeat screening between 24 and 28 WG. The proportion of women with GDM was not specified in the study population. Brachial plexus lesions were reported in 4/154 newborns of mothers with GDM, and with a birth weight > 4,000 g (2.6%), compared to 2/500 newborns of mothers with GDM, but with a birth weight < 4000 g (0.2%), giving an OR of 41.89 (4.05-433.64). In women without GDM, the rate of brachial plexus injuries was 0.1% for infants < 4,000 g and 0.7% for macrosomic infants, with an OR of 6.65 (2.90-15.27) [49] (EL2).

In a retrospective study analysing 303 newborns weighing > 4,000 g, 1.3% of infants suffered brachial plexus injuries, and 6% had humeral or clavicle fractures [16]. Among the 41 newborns of diabetic mothers, there were no brachial plexus injuries and only one fracture (2.4%). Out of the 262 newborns of non-diabetic mothers, four had brachial plexus injuries (1.5%) and 17 had a fracture (6.5%). In terms of birth injuries, there was no significant difference between the two groups.
• Birth injuries and brachial plexus injuries are rarely associated with GDM.
• An increased risk of birth injuries in cases of untreated GDM has not been demonstrated; this is a rare occurrence and the results are discordant.
• The risk seems to be mainly associated with macrosomia (NP2).

7. Neonatal respiratory distress

It is generally recognised that newborns of diabetic mothers are more at risk of developing neonatal respiratory distress. There are three possible causes: premature birth; surfactant deficiency; and caesarean section, which increase the risk of respiratory distress, particularly of transient tachypnea due to delayed resorption of lung fluid [50] (EL2).

It is difficult to know the extent to which prematurity is associated with GDM. Many teams are quick to adopt an interventionist approach in cases of GDM through induced labour or caesarean section [51]. This approach, aimed at preventing late foetal death and shoulder dystocia in cases of macrosomia, is controversial [4] and increases the risk of neonatal respiratory distress.

Two studies have specifically analysed the risk of spontaneous premature birth [52, 53]. In a cohort study of more than 46,000 pregnancies (after exclusion of women with pregestational diabetes), the risk of spontaneous preterm delivery increased with the level of maternal blood glucose, independently of any perinatal complications associated with prematurity. The RR was 1.42 (1.15-1.77) for GDM pregnancies [52] (EL2). One single-centre retrospective study included 1,526 singleton pregnancies with GDM and compared the rate of premature births with a group of 10,560 non-diabetic pregnancies [52] (EL1). The rate of premature births was 10.7% versus 11.3%, P = 0.2. However, mean blood glucose values were higher among GDM patients who delivered prematurely. The risk of spontaneous prematurity was higher when mean blood glucose was > 1.05 g/L (≥ 5.8 mmol/L) (OR = 1.94 [1.25-3.0]) [53].

In the study by Ostlund et al., premature delivery before 37 WG was more common in women with GI (11.4% versus 5.4%, P = 0.005) and was one of the main causes of NICU admission. After adjustment for other prematurity-related risk factors (hypertension, pre-eclampsia, maternal BMI), hyperglycaemia was a risk factor for premature birth < 37 WG (OR = 2.0 [1.0-3.9]) [7] (EL2). The risk of delivery before 37 WG is also thought to be influenced by excessive weight gain during pregnancy [24] (EL2).

Delayed appearance of phosphatidylglycerol (PG), an important component of surfactant, in the amniotic fluid after 34 WG has been found in women with poorly-managed compared to well-managed diabetes. One prospective case-control study included 621 diabetic women (type not specified). The level of glucose control was considered good in 261 subjects (mean blood glucose < 1.05 g/L [< 5.8 mmol/L]), and poor in 360 subjects (mean blood glucose > 1.05 g/L). After stratification by gestational age, the risk of absence of PG in the amniotic fluid was higher in the poor glycaemic control group (OR = 1.83 [1.19-2.84]). This risk was particularly high between 36 and 37 WG (OR = 2.04 [1.1-3.9]). There were no cases of hyaline membrane disease beyond 37 WG [54]. There was no difference in the rate of other types of respiratory distress, such as transient tachypnea, between the two groups. The caesarean rate was not given in this study (EL3).

In another case-control study, pulmonary maturation was compared between a group of 590 pregnant women without diabetes (control), and 295 with diabetes, 74% of which had GDM and 26% had pre-existing diabetes. There was a longer delay in pulmonary maturation, evaluated by the appearance of PG in the amniotic fluid, in all cases of diabetes, but the delay was more pronounced for pre-existing diabetes: 35.9 ± 1.1 weeks for control subjects, 37.3 ± 1.0 weeks for GDM and 38.7 ± 0.9 weeks for pregestational diabetes. Delayed PG synthesis was not related to foetal sex, quality of maternal glucose control or foetal macrosomia [55] (EL3).

The rate and risk of respiratory distress in cases of GDM are difficult to estimate because they are rarely reported in randomised studies comparing treatment strategies. In the study by Crowther et al., (ACHOIS), the risk of respiratory distress, defined by the need for supplemental oxygen beyond four hours after birth, did not increase in the absence of treatment (OR = 1.52 [0.86-2.71], P = 0.15) [41] (EL1). The criterion generally evaluated in randomised studies is transfer to NICU, which indicates the need for special respiratory distress treatment in certain cases. The transfer rate reported varies from 3 to 12%, and does not differ according to the type of GDM treatment [5] (EL1).

In the study by Ostlund et al., the rate of admission to NICU for at least two days was significantly higher for infants born to mothers with GI (18.6% versus 6.3%, P < 0.001). The reasons for this high rate of hospitalisation are likely to be complex. Although infants born to mothers with GI were no more likely to present transient tachypnea, (1.8% versus 1.4%), they were more often born by caesarean (26.4% versus 14.7%, P < 0.001) [7] (EL2). However, the rate of other types of respiratory distress, particularly hyaline membrane disease, was not specified.

In the study by Esakoff et al. of over 36,000 pregnant women with GDM, there was a particularly high risk of respiratory distress in newborns with a birth weight > 4,000 g, compared to those with a birth weight of less than 4,000 g (OR = 3.1 [1.11-8.65]) [49] (EL2).

• A relationship between GDM and neonatal respiratory problems cannot be established due to insufficient data.
• There appears to be an increased risk of respiratory distress in macrosomic infants born to mothers with GDM (NP2).
8. Neonatal metabolic complications

8.1. Hypoglycaemia

For this subject, readers can refer to chapter “Management of infants born to mothers with gestational diabetes”, which deals with the screening and management of hypoglycaemia, and discusses the issue over the definition of hypoglycaemia.

Neonatal hypoglycaemia can be caused by the persistence of foetal hyperinsulinism after birth, particularly when GDM is poorly managed. Hyperinsulinism persists after birth and, in the absence of glucose supply, results in prolonged hypoglycaemia with varying degrees of severity. Insulin inhibits the activation of metabolic pathways of glucose production (glycogenolysis, neoglucogenesis and lipolysis), which occurs naturally in health newborns, and increases glucose consumption by tissues. Polyglobulia reportedly increases the risk of hypoglycaemia [56].

The other cause of neonatal hypoglycaemia is maternal hyperglycaemia during labour, which stimulates the persistent excessive secretion of foetal insulin 1 to 2 hours after birth. A prospective study of 85 women with GDM, 54 of which were treated with insulin, evaluated the effect of controlling maternal blood glucose levels on neonatal hypoglycaemia (two or more blood glucose values < 0.3 g/L [1.7 mmol/L]) [57]. After logistical regression, maternal glycaemia in the last two hours of labour was related to neonatal hypoglycaemia (p < 0.05). It is sometimes recommended to monitor maternal glycaemia every hour during labour, and to maintain levels between 0.7 and 1.2 g/L (4.7 mmol/L) [4]. A discussion on the benefits of maternal glycaemic control and recommended strategies in the delivery room can be found in chapter “Delivery: term, method, intrapartum glycaemic control, anaesthesia”.

The exact incidence of hypoglycaemia in cases of GDM is difficult to assess due to the variable definitions in the different studies. It is also difficult to evaluate the risk in healthy newborns because the majority of studies have included patients retrospectively. The monitoring of newborns is probably subject to certain biases, since those born to diabetic mothers benefit from increased monitoring of their blood glucose at birth [58].

Two randomised studies have evaluated the effect of specific treatment versus routine care, and found a comparable rate of intravenously treated hypoglycaemia (7% versus 5%, p = 0.16 [41] and 5.3% versus 6.8%, P = 0.32 [47]) (EL1). However, the indication for intravenous treatment was not specified in either of these studies. In the second study, the rate of hypoglycaemia defined by a value < 0.35 g/L (1.9 mmol/L) was comparable in both groups (16.3% versus 15.4%, P = 0.75) [47] (EL1).

In the case-control study by Langer et al. of 555 women with untreated GDM diagnosed after 37 WG, 1,110 with treated GDM and 1,110 non-diabetic control subjects, the rates of hypoglycaemia for the three groups were 18%, 6% and 2% respectively, with an OR of 10.38 (6.51-16.56) for untreated GDM versus the control group [6]. The diagnostic strategies differed between the groups: infants of non-diabetic mothers received basic clinical monitoring; infants of diabetic mothers underwent systematic capillary glucose monitoring at least three times during the first hour of life and every half hour until four hours of life. Hypoglycaemia was defined by two consecutive blood glucose values < 0.4 g/L (< 2.2 mmol/L).

In the study by Ostlund et al., the rate of hypoglycaemia, defined by blood glucose < 0.4 g/L (2.2 mmol/L), was higher in the GI group (7.1% versus 2.5%, P = 0.001) [7]. The strategies used to screen for hypoglycaemia were not specified.

It appears that the risk of hypoglycaemia is even higher if the infant is macrosomic. In the study by Esakoff of pregnancies in women with GDM, there was a higher risk of hypoglycaemia in newborns with a birth weight > 4,000 g, compared to those with a birth weight of less than 4,000 g (OR = 2.6 [1.05-6.45]) [49]. However, the incidence of hypoglycaemia (defined by blood glucose < 0.35 g/L [1.95 mmol/L] or plasma glucose < 0.4 g/L [2.2 mmol/L]) was relatively low in both groups (2.6% and 5.3% respectively, p = 0.04) (EL2).

- It is difficult to gauge the risk of neonatal hypoglycaemia in cases of GDM due to the variable definition of hypoglycaemia across studies, and the different monitoring strategies used in the two treatment groups being compared.
- According to the different studies, there is a low rate of hypoglycaemia requiring intravenous therapy (around 5%) (NP1).
- Macrosomia and poor peripartum control of maternal glycaemia are both risk factors for neonatal hypoglycaemia (NP2).

8.2. Hypocalcaemia

Hypocalcaemia has been cited as a complication of maternal diabetes in older studies which do not distinguish between GDM and pregestational diabetes [59]. It has not been studied in more recent publications evaluating the complications according to the strategy used to treat GDM [5]. For the same reasons as for hypoglycaemia, the rate and risk of hypocalcaemia are impossible to evaluate in cases of GDM.

A randomised trial specifically studied the risk of neonatal hypocalcaemia in women with pregestational insulin-dependent diabetes [60]. The patients were divided into two groups: one with strict control of fasting and postprandial blood glucose (n = 68); the other with customary control (n = 69). The results revealed a lower rate of hypocalcaemia in the strict control group (17.6 versus 31.9%, p < 0.05). Calcium concentration was positively correlated with maternal magnesium concentration, and negatively correlated with the HbA1c levels [60] (EL1).
Confusion factors like prematurity [61] or perinatal asphyxia [62] can contribute to low calcium levels.

No study has specifically evaluated the risk of hypocalcaemia in infants born to mothers with GDM. In a cohort study of 530 newborns of diabetic mothers, three infants out of 332 (< 1%) born to mothers with GDM controlled by diet only or by insulin had hypocalcaemia (total calcium concentration < 1.5 mmol/L or ionised calcium concentration < 1.00 mmol/L) [63] (EL4).

8.3. Hyperbilirubinemia

Hyperbilirubinemia has been traditionally studied as a neonatal complication of maternal diabetes, in the same way as other more serious events such as death or brachial plexus injuries. Hyperbilirubinemia is not a serious complication if non-toxic levels are treated, which is usually the case. The danger is the risk of nuclear icterus, which is not classically reported in cases of diabetes. Few studies have demonstrated a difference in the rate and severity of icterus according to the treatment used for diabetes. In the study by Crowther et al., (ACHOIS), the proportion of infants with icterus requiring phototherapy was 9% in both the treatment and the routine-care group (RR = 0.93 [0.63-1.37], p = 0.98) [41] (EL1). In the study by Landon et al., there was no difference in the rate of hyperbilirubinemia between the two treatment groups: 9.6% in the treatment group versus 12.9% in the control group (RR = 0.93 [0.63-1.37], p = 0.98) [41] (EL1). In the HAPO study, hyperbilirubinemia was weakly associated with maternal blood glucose levels at one hour using the 75 g test (OR = 1.11 [1.05-1.17]) and at two hours (OR = 1.08 [1.02-1.13]) [19] (EL2).

- **There seems to be a very low risk of neonatal hypocalcaemia in cases of GDM (< 1%)** (EL4).
- **There is no significant increase in the risk of hyperbilirubinemia in cases of GDM** (EL1).

9. Conclusions

Macrosomia (or excessive foetal growth) is the predominant neonatal adverse outcome in cases of GDM. It is the main factor linked to reported cases of complications in GDM.

Maternal obesity is an additional risk factor for complications, regardless of diabetes status.

Serious perinatal complications (malformations and perinatal deaths) reported in studies on GDM appear to be attributable to undiagnosed pre-pregnancy type 2 diabetes.

10. Conflict of interests

No conflict of interests related to the article.

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