Maternal outcome of gestational diabetes mellitus

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Abstract

Objective: To estimate maternal outcome of treated or untreated gestational diabetes mellitus (GDM).

Methods: French and English publications were searched using PubMed and the Cochrane library.

Results: The diagnosis of GDM includes a high risk population for preeclampsia and Caesarean sections (EL3). The risks are positively correlated with the level of hyperglycaemia in a linear way (EL2). Intensive treatment of mild GDM compared with routine care reduces the risk of pregnancy-induced hypertension (preeclampsia, gestational hypertension). Moreover, it does not increase the risk of operative vaginal delivery, Caesarean section and postpartum haemorrhage (EL1). Being overweight, obesity and maternal hyperglycaemia are independent risk factors for preeclampsia (EL2). Their association with GDM increases the risk of preeclampsia and Caesarean section compared to diabetic women with a normal body mass index (EL3). The association of several risk factors (such as advanced maternal age, pre-existing chronic hypertension, pre-existing nephropathy, obesity, suboptimal glycaemic control) increases the risk of preeclampsia. In that case, the classic follow-up (blood pressure measurement, proteinuria) should be more frequent than monthly (professional consensus). The risk of Caesarean section is increased by macrosomia, whether suspected prenatally or not, but this increased risk remains whatever the birth weight (EL3). Diagnosis and treatment of GDM do not reduce the risk of severe perineal lesions, operative vaginal delivery and postpartum haemorrhage (EL2). Some psychological symptoms, such as anxiety and alteration of self-perception, can occur upon diagnosis of GDM (EL3). The treatment of GDM appears to reduce the risk of postpartum depression symptoms (EL2).

Conclusion: Most of the information published on GDM covers the risks of preeclampsia and Caesarean section; intensive care of GDM reduces these risks. Pregnancy care should be adjusted to the risk factors.

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Keywords: gestational diabetes mellitus, maternal outcome, maternal morbidity, treatment, untreated gestational diabetes, review

Résumé

Complications maternelles du diabète gestationnel

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

Méthodes : Recherche bibliographique en langues française et anglaise effectuée par consultation des banques de données PubMed et Cochrane.

Résultats : Le diagnostic de DG permet d’identifier une population à risque de prééclampsie et de césarienne (NP4). Ces risques sont corrélés de façon positive et linéaire au degré de l’hyperglycémie initiale (NP2). Le traitement intensif du DG modéré permet de réduire le risque de pathologie hypertensive de la grossesse (hypertension artérielle gravidique et prééclampsie) par rapport à une prise en charge usuelle, sans majoration des risques de césarienne, d’extraction instrumentale et d’hémorragie du post-partum (NP1). Le surpoids et l’obésité sont des facteurs de risque de prééclampsie indépendants de l’hyperglycémie maternelle (NP2). Leur association au DG augmente tousjours les risques de prééclampsie et de césarienne par rapport aux femmes diabétiques qui ont un indice de masse corporelle normal (NP3). La présence de facteurs de risque surajoutés (âge maternel élevé, obésité, antécédents d’hypertension artérielle chronique ou de néphropathie, mauvais équilibre glycemique) peut justifier d’un rythme de surveillance (pression artérielle, recherche d’une protéinurie) plus rapproché que le suivi prénatal mensuel classique, en raison des risques accrus de prééclampsie (avis d’expert). En dépit d’une corrélation avec la macrosomie, suspectée ou non en anténatal, le risque de césarienne persiste quel que soit le poids de naissance (NP3). Les risques d’extraction instrumentale, de déchirure péritonéale sévère et d’hémorragie du post-partum ne sont pas influencés par le diagnostic et le traitement du DG (NP2). Des troubles psychologiques à type d’anxiété et d’altération de la perception de soi peuvent être présents au moment du diagnostic de DG (NP3). Le traitement diminuerait le risque de dépression du post-partum (NP2).

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Conclusion: Les données disponibles sur les complications maternelles du DG concernent essentiellement les risques de prééclampsie et de césarienne. Le traitement intensif du DG permet de réduire ces risques. La surveillance de la grossesse doit être adaptée en fonction de la présence de facteurs de morbidité associés.

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Mots clés: diabète gestationnel, complications maternelles, pronostic maternel, traitement, diabète gestationnel non traité, revue

1. Introduction

Gestational diabetes mellitus (GDM) is a glucose tolerance problem and hyperglycaemia of variable severity, beginning or diagnosed for the first time during pregnancy, whatever the treatment course and post partum evolution may be [1]. This definition poses several problems in evaluating risks of maternal complications during pregnancy.

It includes the possibility of a prior glucose tolerance problem before pregnancy that went unrecognized (most often type 2 diabetes) for which the maternal/fetal prognosis is much more reserved than for that of transitory hyperglycaemia with onset in the second half of pregnancy and disappearing after delivery [2, 3]. Both these situations share the same physiopathology (insulin resistance and inadequate production of insulin) [4] and common risk factors [5].

There is a positive, linear correlation with no real threshold between risks for gestational complications and maternal glycaemia, which gives rise to problems in diagnosing GDM [3, 6].

GDM and type 2 diabetes share the same risk factors (advanced maternal age, insulin resistance and obesity) and are themselves independent risk factors for pregnancy related complications (preeclampsia, to name one) and Caesarean sections [4]. This gives rise to some confusion when evaluating maternal risks inherent to GDM. The aim of this literature study is to determine if treated or untreated GDM is associated with an increase in maternal complications.

2. Methodology

The bibliographical research was carried out over a period from January 1995 to June 2010 with help from the Medline and Cochrane Library databases. It covers all the studies on maternal complications in GDM.

The research terms came either from a thesaurus (MeSH descriptor for Medline), or taken from a title or abstract (key words). They were combined in as many steps necessary using the words “AND,” “OR,” and “EXCEPT”.

The key words tested are as follows: gestational diabetes, gestational diabetes mellitus, pregnancy complications, pregnancy outcome, untreated gestational diabetes, preeclampsia, gestational hypertension, pregnancy-induced hypertension, thromboembolic disease, preterm birth, Caesarean section, operative delivery, obesity. The MeSH terms tested are as follows: “Diabetes, gestational,” “Pregnancy Complications”.

Only publications in English and French were retained. They were sorted by level of proof: meta-analyses controlled randomized studies, non randomized controlled studies and cohort studies. Several abstract journals were consulted. Computer searches were completed by a manual search of references in the selected articles.

The recommendations of the following learned societies were consulted: Haute Autorité de Santé (HAS) www.has-sante.fr/publications; National Institute for Health and Clinical Excellence (NICE) www.nice.org.uk; Royal College of Obstetricians and Gynaecologists (RCOG) www.rcog.org.uk; American College of Obstetricians and Gynecologists (ACOG) www.acog.org; Society of Obstetricians and Gynaecologists of Canada (SOGC) www.sogc.org; Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) www.ranzcog.edu.au.

3. Link between hyperglycaemia and maternal prognosis

In several cohort studies on patients defined as non diabetic (glycaemia below retained thresholds for GDM), and thus untreated, there was a linear link (continuum) between maternal glycaemia (measured between 24 and 28 weeks gestation (WG) fasting and/or after a 50g or 75g oral glucose tolerance test) and onset of perinatal and maternal complications (Caesarean sections and preeclampsia) after adjusting for several confusion factors (age, ethnicity, body mass index, weight gain and parity) [7-11] (EL3).

The prospective multicentre observational study HAPO (Hyperglycaemia and Adverse Pregnancy Outcome) carried out on over 25,000 pregnant women of different ethnic backgrounds sought to establish a link between maternal hyperglycaemia and maternal/fetal outcome in order to define the best intervention threshold from glycaemia measured between 24 and 32 WG fasting, at 1 and 2 hours after a 75g dose of glucose solution [12]. The study observed that glycaemia values had a positive and linear correlation with rates
of Caesareans (primary judgment criterion) and preeclampsia (secondary judgment criterion) and were much lower than those usually chosen as diagnostic criteria for GDM. The link between hyperglycaemia and maternal prognosis remained after adjusting for confusion factors (centre, age, ethnicity, parity, body mass index, average blood pressure). Secondary analyses could not determine threshold values given the continuity observed in the results [12] (EL2).

In cases of glucose intolerance defined by a positive screening test (after a 50g dose of glucose solution) and a negative diagnostic test (after 75g or 100g dose glucose solution), maternal complications do not appear to increase compared to a control population defined by a negative screening test, after adjusting for confusion factors (age, body mass index). According to the studies, the judgment criteria evaluated were either composite criteria integrating several severe maternal complications (death, eclampsia, renal failure, stroke) [13], or a single criterion (Caesareans, gestational hypertensive complications, infections, post partum haemorrhages) [11, 13] (EL3). In cases of glucose intolerance, defined by a positive screening test (after 50g glucose solution) and a diagnostic test with a single abnormal value (after 100g glucose solution) according to the Carpenter Coustan criteria, the results of case-control studies are discordant on the risk of gestational hypertensive complications [14] (EL3). The data are not sufficient enough to say if there is an increased maternal risk in cases of glucose intolerance defined by a positive screening test (O’Sullivan) associated with a negative diagnostic test (less than two abnormal values) (EL3).

**Overall, there is a positive, linear correlation between the degree of maternal hyperglycaemia and the risk of preeclampsia and Caesarean delivery, though no discriminating threshold can be defined (EL2).**

4. Maternal prognosis with GDM compared to a control population

Given the continuum between the level of hyperglycaemia and prognosis, the risks of maternal complications vary according to the diagnostic criteria chosen in the studies.

4.1. Untreated GDM (case-control studies)

That fact that GDM is not treated implies that it was neglected or unrecognized throughout a pregnancy or discovered late, generally after 36 WG.

There are few case-control studies that have evaluated the prognosis of untreated GDM; they are presented in Table 1 [15-19]. They are most often retrospective, with various methodologies, of limited power and the maternal criteria studied are limited to Caesareans or preeclampsia rates. The results do not help elucidate if untreated GDM is at the origin of an increase in maternal complications compared to a non diabetic population. There does however seem to be an increase in the rate of Caesareans. [18] (EL4).

4.2. Treated GDM (case-control studies)

Cohort studies comparing maternal outcome in cases of treated GDM compared to a control population are also presented in Table 1 [20-32]. Aside from risks of gestational hypertensive complications and Caesarean sections, judgment criteria for pregnancy and birth have rarely been evaluated. The retrospective nature of the data collected, the heterogeneity of the diagnostic criteria and the low number of cohorts also limit the level of proof of results. They suggest that preeclampsia and Caesarean risks remain despite treatment compared to a non diabetic population (EL4). These risks appear to be correlated with the level of hyperglycaemia before treatment and remain after adjusting for confusion factors (Table 1) [33, 34].

A Danish retrospective, multicentre cohort study (n = 3260) compared the prognosis of four groups established according to glycaemia measured 2 hours after a 75 g dose of glucose: < 1.40 g/L (7.8 mmol/L) [control group], 1.40-1.60 g/L (7.8-8.9 mmol/L) [glucose intolerance], 1.61-2 g/L (9-11 mmol/L) and over 2 g/L (11.1 mmol/L) [33]. Only patients from the last two groups were considered to be diabetic and treated. A multivariate analysis after adjusting for confusion factors (BMI before pregnancy, age, ethnic origin, tobacco use, weight gain during pregnancy, care centre, birth term) observed a significant increase in the risk in pregnancy, including hypertensive complications (preeclampsia and gestational hypertension), only in the group with over 2 g/L (treated) compared to the control group (10.4 versus 6.1%; OR: 2.9, CI 95% [1.3-6.2]). The Caesarean rate was not changed with glycaemia. The rate of spontaneous preterm labour also increased in cases of glycaemia > 2 g/L (13.4 versus 2.8%; OR: 5.1, CI 95% 2.4-11.0) [33] (EL4).

An Australian retrospective cohort study (n = 16,975) evaluated prognosis with fasting glycaemia and 2 hours after a 75g dose of glucose, given if the 50g screening test was positive [34]. The GDM diagnostic criteria were fasting glycaemia > 1.26 g/L (7 mmol/L) and/or at 2 hours > 2 g/L (11.1 mmol/L). Values that defined a glucose intolerance (called “moderate” GDM by the authors) were fasting glycaemia between 1 (5.5 mmol/L) and 1.26 g/L (7 mmol/L) or over 2 g/L (11.1 mmol/L). Treatment was given to both these patient groups. The progressive increase in glycaemia observed during the 50g screening test (< 1.40 g/L; 1.40-2 g/L and > 2 g/L) was associated with a significant increase in preeclampsia rates (respectively 7%, 10.3% and 19.3%, p < 0.001) and Caesarean rates (respectively 21.7%, 31% and 37.7%, p < 0.001). However, preeclampsia rates only increased compared to the control group when fasting glycaemia was between 1 and 1.26 g/L (20.1% versus 10.3%,
Table 1
Maternal outcome comparison between untreated or treated gestational diabetes and control group (cohort studies).

<table>
<thead>
<tr>
<th>Study, year, country</th>
<th>Type of study</th>
<th>GDM diagnostic criteria</th>
<th>GDM prevalence</th>
<th>Results Cohort/Control</th>
<th>P value or adjusted OR (CI 95 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated GDM</strong></td>
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<tr>
<td>Adams, 1998, USA [15]</td>
<td>Case-control</td>
<td>Universal screening NDDG criteria</td>
<td>16/64</td>
<td>Caesareans 25 vs. 16%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>Pairing for age, ethnicity, parity, BMI, weight gain, birth term</td>
<td></td>
<td>Caesareans for dystocia 19 vs. 16%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Single centre</td>
<td></td>
<td></td>
<td>OVD 19 vs. 19%</td>
<td>NS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectal lesions 13 vs. 6%</td>
<td>NS</td>
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<tr>
<td>Yang, 2002, China [16]</td>
<td>Case-control</td>
<td>2-stage universal screening 75g OGGT Criterias: FG &gt; 1.40 g/l at 2 h &lt; 2 g/l</td>
<td>102/302</td>
<td>PE 19.6 vs. 6.6%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>Adjusted for age, parity, BMI, care centre</td>
<td></td>
<td>PROM 13.7 vs. 2%</td>
<td>10 (2.9-34.9)</td>
</tr>
<tr>
<td></td>
<td>Multicentre</td>
<td></td>
<td></td>
<td>PL 7.8 vs. 1.3%</td>
<td>6.4 (1.46-28)</td>
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<td></td>
<td>Caesareans 73 vs. 66%</td>
<td>NS</td>
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<tr>
<td>Ostlund, 2003, Sweden [17]</td>
<td>Case-control</td>
<td>2-stage universal screening 75g OGGT Criterias: FG &lt; 1.20 g/l and 1.60 g/l at 2 h &lt; 2 g/l</td>
<td>213/812</td>
<td>GH 2.4 vs. 1.7%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>Adjusted for parity, ethnicity, BMI, birth weight, gestational hypertension</td>
<td></td>
<td>PE 4.7 vs. 2.7%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Multicentre</td>
<td></td>
<td></td>
<td>Caesareans 26 vs. 15%</td>
<td>1.9 (1.2-2.9)</td>
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<td></td>
<td>Emergency</td>
<td>2.1 (1.3-3.5)</td>
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<td></td>
<td>Caesareans 17 vs. 10%</td>
<td>NS</td>
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<td></td>
<td></td>
<td></td>
<td>OVD 7.5 vs. 7.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Langer, 2005, USA [18]</td>
<td>Case-control</td>
<td>2-stage screening Carpenter Coustan criteria</td>
<td>555/110</td>
<td>Caesareans 24 vs. 14%</td>
<td>1.88 (1.45-2.43)</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>Pairing for BMI, parity, ethnicity, birth term and type of care</td>
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<td></td>
<td>Single centre</td>
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<tr>
<td>Kwik, 2007, Australia [19]</td>
<td>Case-control</td>
<td>Single screening 75g OGGT Criterias: FG &gt; 1.40 g/l at 2 h &lt; 1.55 g/l</td>
<td>213/197</td>
<td>PE 11.7 vs. 5.1%</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>Induced labour 28 vs. 20%</td>
<td></td>
<td>Caesareans 29 vs. 31%</td>
<td>NS</td>
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<tr>
<td></td>
<td>Multicentre</td>
<td></td>
<td></td>
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<td>P &lt; 0.05</td>
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<tr>
<td><strong>Treated GDM</strong></td>
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<tr>
<td>Casey, 1997, USA [20]</td>
<td>Retrospective</td>
<td>2-step selective screening NDDG criteria</td>
<td>874/61 209</td>
<td>GH 17 vs. 12%</td>
<td>P = 0.001</td>
</tr>
<tr>
<td></td>
<td>Population from a perinatal database</td>
<td>Pairing for age, ethnicity, weight and parity</td>
<td></td>
<td>Induced labour 14 vs. 10%</td>
<td>P = 0.001</td>
</tr>
<tr>
<td></td>
<td>Single centre</td>
<td></td>
<td></td>
<td>Caesareans 30 vs. 17%</td>
<td>P &lt; 0.001</td>
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<td>OVD 5 vs. 6%</td>
<td>NS</td>
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<tr>
<td>El Mallah, 1997, Saudi Arabia [21]</td>
<td>Case-control</td>
<td>Universal screening NDDG criteria</td>
<td>972/904</td>
<td>PE 2 vs. 0.9%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>No Pairing prevalence 9.8%</td>
<td></td>
<td>Caesareans 17 vs. 7.5%</td>
<td>P &lt; 0.001</td>
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<tr>
<td></td>
<td>Single centre</td>
<td></td>
<td></td>
<td>Perineal tearing 18 vs. 10.7%</td>
<td>P &lt; 0.001</td>
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<td>PPH 1.75 vs. 1.75%</td>
<td>NS</td>
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<tr>
<td>Jensen, 2000, Denmark [22]</td>
<td>Case-control</td>
<td>Selective screening 75g OGGT Criterias: FG &gt; 1.10 g/l and/or G at 2 h &gt; 1.64 g/l</td>
<td>143/143</td>
<td>Preeclampsia (PE, CH or GH) 20 vs. 11%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>Pairing for age, parity and BMI</td>
<td></td>
<td>Induced labour 61 vs. 24%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Single centre</td>
<td></td>
<td></td>
<td>Caesareans 33 vs. 21%</td>
<td>P = 0.03</td>
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<td></td>
<td>PL 11 vs. 5%</td>
<td>NS</td>
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<tr>
<td>Xiong, 2001, Canada [23]</td>
<td>Retrospective</td>
<td>Universal screening NDDG criteria</td>
<td>N = 111 419</td>
<td>GH 11 vs. 5%</td>
<td>1.26 (1.21-1.32)</td>
</tr>
<tr>
<td></td>
<td>Population from a collective database of 39 maternity wards</td>
<td>2755 GDM (2.5%)/108 664 non GDM</td>
<td></td>
<td>PE 3 vs. 1%</td>
<td>1.30 (1.20-1.41)</td>
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<td>CH 1 vs. 0.7%</td>
<td>0.99 (0.87-1.13)</td>
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<td>PROM &lt; 37 WG 4.6 vs. 3.3%</td>
<td>1.13 (1.06-1.20)</td>
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<td>Caesareans 25 vs. 16%</td>
<td>1.13 (1.10-1.17)</td>
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<td></td>
<td>PL 10.4 vs. 7.5%</td>
<td>1.13 (1.08-1.18)</td>
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<tr>
<td>Lao, 2001, China [24]</td>
<td>Observational</td>
<td>Universal screening 75g test WHO criteria</td>
<td>67/209</td>
<td>PE 12 vs. 2.4%</td>
<td>4.6 (2-11)</td>
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<tr>
<td></td>
<td>Prospective</td>
<td>Prevalence 13.7 %</td>
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<td>Caesareans 13.4 vs. 7.7%</td>
<td>P = 0.05</td>
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<td>Single centre</td>
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<td>OVD 24 vs. 22%</td>
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<td>Spontaneous PL 1.5 vs. 3%</td>
<td>NS</td>
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<tr>
<td>Study, year, country</td>
<td>Type of study</td>
<td>GDM diagnostic criteria</td>
<td>No. patients Cohort/ control</td>
<td>GDM prevalence</td>
<td>Results Cohort/Control</td>
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<tr>
<td>Svare, 2001, Denmark [25]</td>
<td>Case-control Retrospective Single centre</td>
<td>Selective screening 75g OGTT Criteria: FG &gt; 1.05 g/L and/or G at 2 h &gt; 1.60 g/L</td>
<td>327/295 with risk factors of GDM and negative test</td>
<td>PE 7 vs. 4%</td>
<td>P value or adjusted OR (CI 95 %)</td>
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<td>RPH 0 vs. 1%</td>
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<td>Induced labour 44 vs. 12%</td>
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<td>Caesareans 19 vs. 16%</td>
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<td>OVD 7 vs. 10%</td>
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<td>Spontaneous PL 8 vs. 2%</td>
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<td>Van Hoorn, 2002, Australia [26]</td>
<td>Case-control Retrospective Single centre</td>
<td>2-stage universal screening 75 g OGTT Criteria: FG &gt; 1 g/L and/or G at 2 h &gt; 1.46 g/L</td>
<td>51/258</td>
<td>GH 45 vs. 29%</td>
<td>PE 19.6 vs. 17.1%</td>
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<td>Caesareans 31 vs. 25%</td>
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<td></td>
<td>OVD 27.4 vs. 25.6%</td>
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<tr>
<td>Stone, 2002, Australia [27]</td>
<td>Retrospective Population from a regional database Multicentre</td>
<td>Undefined</td>
<td>2169/58 231 Adjusted for age, parity, ethnic origin Prevalence 3.6%</td>
<td>GH and CH 11.6 vs. 7.6%</td>
<td>PE 8 vs. 5%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>RPH 0.5 vs. 0.7%</td>
<td>Induced labour 37 vs. 23%</td>
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<td>Caesareans 32 vs. 19%</td>
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<td></td>
<td>Emergency Caesareans 12 vs. 8%</td>
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<td></td>
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<td></td>
<td></td>
<td>OVD 41 vs. 29%</td>
<td></td>
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<tr>
<td>Vivet-Lefebure, 2007, France [28]</td>
<td>Case-control Retrospective Bi-centre</td>
<td>Universal screening Carpenter Coustan criteria</td>
<td>1172/1172 Pairing for age and parity Prevalence 7.5%</td>
<td>PE 2.2 vs. 2.7%</td>
<td>Obstetrical vascular disease 6.2 vs. 4.4%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CH 5.3 vs. 3.3%</td>
<td>Induced labour 31 vs. 21%</td>
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<td></td>
<td></td>
<td></td>
<td>Caesareans 28 vs. 18%</td>
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<td></td>
<td></td>
<td></td>
<td>Emergency Caesareans 10.6 vs. 8.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OVD 6.4 vs. 8.7%</td>
<td></td>
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<tr>
<td>Lapolla, 2009, Italy [29]</td>
<td>Prospective Multicentre Population from a collective database of 31 maternity wards</td>
<td>Universal screening Carpenter Coustan criteria</td>
<td>3465/367 932 Control population from national Italian perinatal registry</td>
<td>GH 6.5%</td>
<td>PE 1.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caesareans 35 vs. 33%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PL 8.8 vs. 5.8%</td>
<td></td>
</tr>
<tr>
<td>Karmon, 2009, Israel [30]</td>
<td>Retrospective Population from a database Single centre</td>
<td>Universal screening Carpenter Coustan criteria</td>
<td>10 227/174 029 Prevalence 5.6%</td>
<td>Gestational hypertensive complications (PE, CH or GH) 11.6 vs. 5.5%</td>
<td>RPH 0.8 vs. 0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Induced labour 42 vs. 27%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Caesareans 23 vs. 12%</td>
<td></td>
</tr>
<tr>
<td>Peticca, 2009, Canada [31]</td>
<td>Retrospective Population from a regional database Multicentre</td>
<td>Undefined</td>
<td>3 188/115 996 Adjusted for age, parity, tobacco use and type of care</td>
<td>Gestational hypertensive complications (PE, CH or GH) 9 vs. 4.6%</td>
<td>Induced labour 38 vs. 24%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Caesareans 38 vs. 28</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PL 11.3 vs. 8.4%</td>
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</tbody>
</table>
RR: 1.95; CI 95% [1.34-2.83]) or glycaemia at 2 hours at 2 g/L (19.7% versus 10.5%, RR: 1.87, CI 95% [1.05-3.32]). Caesarean rates were not modified according to the values for fasting glycaemia and glycaemia at 2 hours. ROC curves established did not help determine a sufficiently pertinent hyperglycaemia threshold value in terms of sensitivity and specificity for predicting preeclampsia and Caesarean section [34] (EL4).

4.3. Maternal prognosis according to diagnostic criteria selected

Two retrospective studies observed that the Carpenter-Coustan criteria had better sensitivity for determining risks for Caesarean sections and operative vaginal deliveries than those by the NDDG, whereas risks for gestational hypertensive complications and birthing complications (severe perineal lesions, post partum haemorrhages) were the same no matter which diagnostic criteria used [35, 36] (EL4). However, a Spanish retrospective series did not observe any differences in maternal complication rates, be it with the Carpenter-Coustan or NDDG criteria [37] (EL4). In a Brazilian cohort tested with 75g glucose, the sensitivity of the WHO and the American Diabetes Association diagnostic criteria concerning preeclampsia were also the same [38] (EL4). As far as we know, there are no studies that have compared maternal prognosis according to the results of the glucose challenge test (75 or 100g).

No diagnostic method for GDM has proven its superiority in terms of predicting risks of maternal complications (EL4).

4.4. Controlled randomized studies

Despite the close link between the degree of maternal hyperglycaemia and onset of perinatal complications, there are only two recent randomized studies that have shown that active treatment helps reduce the risk of maternal complications, particularly preeclampsia, though GDM was only moderate [39, 40]. These two trials compared a treatment group (diet, surveillance of capillary glycaemia and insulin therapy, if needed) to a control group only receiving the usual prenatal care (the patients and caregivers did not know about the GDM). Table 2 summarizes the methodology of their primary results. They are in favour of intensive treatment for moderate GDM to reduce risks of gestational hypertension or excessive weight gain [39, 40] (EL1). By extrapolation, it can be estimated that active and early care is of probable interest in cases of more severe hyperglycaemia. It should be noted that the study by Landon et al. included a majority of obese women (average BMI 30 kg/m²), thus demonstrating that treatment has an impact, especially in cases of high BMI by limiting excessive weight gain [40].

A meta-analysis from 2009 for the Cochrane Database [41] compiled eight randomized studies (1,418 patients), five of which compared intensive treatment of GDM to habitual care (Table 2). This meta-analysis noted a decrease in the rate of preeclampsia and an increase in the rate of induced labour in cases of intensive treatment, but the statistical weight of the ACHOIS study was evident (1,000 patients). Furthermore, the judgment criterion for preeclampsia in this trial was gestational hypertension and not preeclampsia (two measurements of systolic and diastolic blood pressure over 140/90 mmHg without knowing if proteinuria was present or not). The conclusions of this meta-analysis can therefore not be retained for this criterion. However, there was no significant difference concerning the other maternal variables studied (Caesarean sections, operative vaginal delivery and post partum haemorrhage) [41] (EL1).

A meta-analysis published in 2010 selected five randomized studies comparing treatment of GDM to habitual care to evaluate the risks of preeclampsia [42]. The authors included the results of the study by Landon et al. [40] but not those from the ACHOIS study because the judgment criterion was gestational hypertension and therefore could not be
used. The rate of Caesarean sections was not modified by treatment of GDM (4 trials, n = 2,357.28 \textit{versus} 2,330.28) (EL1). In another analysis that compiled 13 randomized studies which compared different specific treatments for GDM, the rates of Caesarean sections and preeclampsia were the same no matter what type of care patients received [42].

### Table 2
Maternal outcome comparison between treated gestational diabetes mellitus and control group (randomized studies).

<table>
<thead>
<tr>
<th>Study, year, country</th>
<th>Type of study</th>
<th>Inclusion criteria</th>
<th>No. patients Treatment/Control</th>
<th>Judgement criteria</th>
<th>P value or RR (CI at 95 or 97%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowther, 2005, Australia and United Kingdom [39]</td>
<td>Multicentre</td>
<td>Intention to treat</td>
<td>490/510</td>
<td>Primary Adjusted for age, parity, ethnicity</td>
<td>1.36 (1.15-1.62) NS NS</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>24-34 WG Risk factors for GDM or O’Sullivan &gt; 1.40 g/L 75 g OGGT FG &lt; 1.40 g/L and G at 2 h between 1.40 and 1.98 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landon, 2009, USA [40]</td>
<td>Multicentre</td>
<td>Intention to treat</td>
<td>476/455</td>
<td>Secondary PE 2.5 vs. 5.5% Gestational hypertensive complications (PE and GH) 8.6 vs. 13.6%</td>
<td>0.46 (0.22-0.97) 0.63 (0.42-0.96) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24-31 WG O’Sullivan between 1.35 and 2 g/L 100 g OGGT Carpenter Coustan criteria Except FG &lt; 0.95 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochrane Database, 2009, United Kingdom [41]</td>
<td>Meta-analysis of 8 randomized controlled trials (1418 patients)</td>
<td>Specific treatment/routine prenatal care</td>
<td>PE (1 trial) 12 vs. 18% Caesareans (5 trials) 28 vs. 30%</td>
<td>0.65 (0.48-0.88) NS 1.33 (1.13-1.57) NS</td>
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<tr>
<td></td>
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<td></td>
<td>Induced labour (2 trials) 40 vs. 30% OVD (1 trial) 3 vs. 2.7% PPH (1 trial)</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>Horvath, 2010, Austria, Germany [42]</td>
<td>Meta-analysis of 5 randomized controlled trials</td>
<td>Specific treatment/routine prenatal care</td>
<td>PE (1 trial) 2.5 vs. 5.5% Caesareans (4 trials) 28 vs. 31%</td>
<td>0.46 (0.22-0.97) NS</td>
<td></td>
</tr>
</tbody>
</table>


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**Overall, the diagnosis of GDM helps identify an at-risk population for preeclampsia and Caesarean section (EL4). These risks are correlated with the severity of hyperglycaemia at the time of diagnosis and remain despite treatment and compared to a non diabetic population (EL4).**

**Intensive treatment of moderate GDM helps reduce risks of preeclampsia and excessive weight gain compared to absence of therapy, without increasing risks of Caesarean section, operative vaginal delivery and post partum haemorrhage (EL1). Limiting weight gain in obese women is associated with a reduction in the risk of preeclampsia (EL1).**

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5. Link between GDM and obesity

Numerous cohort studies have observed a positive, significant, independent correlation of maternal glycaemia (exclusion of GDM in the study or after multivariate analysis accounting for confusion factors) between being overweight (mild obesity and obesity) and an increase in risks of pregnancy complications (mainly gestational hypertension, genital and urinary infections and post partum haemorrhage) and in obstetrical interventions (Caesareans and induced labour) [43-47].

The risk of preeclampsia increases along with BMI. A meta-analysis of 13 cohort studies reported a highly significant, independent link of the main confusion factors (age, parity, tobacco use, chronic hypertension, pre-existing diabetes or not, twin pregnancy), between high pre-pregnancy BMI and onset of preeclampsia, with the relative risk doubling for every additional 5-7 kg/m² [45] (EL2). A secondary analysis of the HAPO study also found a highly significant, continuous association, independent of maternal glycaemia and average blood pressure, between the degree of obesity and risk for preeclampsia, with an adjusted OR increasing from, respectively, 1.56 (CI 95% [1.17-2.08]) to 14.14 (CI 95% [9.44-21.17]) for BMI over 22.6 to more than 42 kg/m² [46] (EL2). Obesity is therefore an independent risk factor of maternal complications and a potential source of confusion in evaluating the risks for GDM itself. An excess in fat mass can favour insulin resistance and the secretion of pro-inflammatory markers that easily lead to hyperglycaemia and therefore to an increase in the prevalence of GDM in obese women. It is, however, rather variable (15 to 25%) according to cohort and screening method [48, 49]. A recent meta-analysis compiling 70 observational studies (671,945 patients) evaluated the risk of GDM according to pre-pregnancy BMI after universal screening and excluding pre-existing diabetes [50]. Compared to a normal BMI, the non adjusted OR of developing GDM in cases of mild obesity (BMI between 25 and 29.9 kg/m²), moderate obesity (30 to 34.9 kg/m²) and severe obesity (> 35 kg/m²) were, respectively, 1.97 (1.77-2.19), 3.01 (2.34-3.87) and 5.55 (4.27-7.21), with an increase of 0.92% in the prevalence of GDM (CI 95% [0.3-1.10]) for an increase of 1 kg/m² (EL2).

To our knowledge, maternal prognosis in cases of obesity associated with GDM has only been evaluated in two retrospective case-control studies from the same American team [51, 52] (EL4). It seemed to be correlated more with glycaemic balance than the degree of obesity. Among 4,001 cases of GDM stratified according to pre-pregnancy BMI, the risk of preeclampsia in overweight and obese patients only increased in comparison to women of normal body weight when glycaemic control was poor, despite insulin therapy (relative OR: 2.25, CI 95% [1.29-3.89] and 2.68, CI 95% [1.61-4.48]) [51]. The risk of Caesarean section only increased in cases of diet alone, whether or not glycaemia was under control, whereas onset of insulin therapy did not modify the risk [51]. Among the 1,319 obese women with GDM, the rate of preeclampsia was the same as those with a BMI under 35 kg/m² or higher (11 and12% respectively), with a higher rate of insulin therapy in cases of morbid obesity (62 versus 73%, p = 0.002) and an equal number of women with balanced glycaemia (63 and 61% respectively) [52].

Obesity is also most often associated with the presence of type 2 diabetes [53] and chronic hypertension (30% prevalence, OR 2 to 3, compared to a normal BMI) [49, 51]. The association of these co-morbidity factors increases the risk of maternal complications [54]. It also represents a source of bias and confusion in evaluating the inherent risks of GDM.

In GDM, weight gain during pregnancy judged to be excessive compared to pre-pregnancy BMI could be correlated with a significant increase in certain maternal risks (pre-term labour, Caesarean sections), and remains after adjusting for confusion factors (age, parity, ethnicity, GDM treatment and birth term) [55] (EL4).

6. GDM and gestational hypertension

Maternal risks classically associated with GDM are gestational hypertension (GH), defined as systolic and/or diastolic blood pressure higher than or equal to 140/90 mmHg after 20 WG, and preeclampsia, defined by GH associated with proteinuria higher than or equal to 0.3 g per 24 hr. The causal link between hyperglycaemia and onset of gestational hypertension is difficult to evaluate because numerous confusion factors coexist (advanced age, obesity, chronic hypertension, family history) so that results of cohort studies are contradictory on the increased risk of gestational hypertension in cases of GDM (Table 3) [56-62] (EL3).

By grouping all vascular and gestational complications in one category, some studies found a significant increase in risk in cases of treated GDM compared to the control population [20, 22, 28, 30, 56, 59] (EL3).

6.1. GDM and preeclampsia

Most cohort studies describe a highly significant association between GDM and preeclampsia, which remains after adjusting for confusion factors (Table 1 to 3). Despite the mostly homogeneous definitions, the prevalence of preeclampsia varies considerably (1.4 to 20%), probably in relation to different populations (Tables1 to 3). The international HAPO study found preeclampsia rates that varied depending on centres from 1.4 to 11.4% [12].
A secondary analysis of this observational study showed that there was a significant, continuous association between the risk of preeclampsia and the degree of fasting maternal glycaemia (OR: 1.08, CI 95% [1.00-1.16], at 1 hour (OR: 1.19, CI 95% 1.11-1.28) and at 2 hours (OR: 1.21, CI 95% [1.13-1.30]) with a 75g dose of glucose [63] (EL2). Adjustment for confounding factors (centre, age, parity, inclusion term, family history, BMI measured at inclusion between 24 and 32 WG and fasting plasma levels of peptide C) helped put in perspective the increased risk of preeclampsia in cases of maternal hyperglycaemia (OR between 1.08 and 1.21). It seems modest in cases of GDM not associated with other co-morbidity factors, particularly in the absence of excess weight in mothers to be.

The risk of preeclampsia appears to be correlated with the severity of hyperglycaemia at the time of diagnosis and glycaemic balance after starting treatment. A retrospective American study (n = 1,813) observed an increase in the rate of preeclampsia when fasting glycaemia for the 100g glucose challenge test was higher than 1.05 g/L (14 versus 8%, OR: 1.81, CI 95% [1.3-2.51]) and when glycaemic balance (defined as average glycaemia lower than 0.95 g/L) was not obtained despite treatment (18 versus 10%, OR: 2.56, CI 95% [1.5-4.3]) [64] (EL4). In this series, prior obesity and the severity of GDM were independent risk factors of preeclampsia after multivariate analysis (respective OR: 2.3 CI 95% [1.16-2.30] and 1.7 CI 95% [1.21-2.38]). Among the diabetic women who developed preeclampsia, the obesity rate was higher

Table 3
Correlation between gestational diabetes mellitus and gestational hypertensive pathologies (gestational hypertension and pre-eclampsia).

<table>
<thead>
<tr>
<th>Study, year, country</th>
<th>Type of study</th>
<th>GDM diagnostic criteria</th>
<th>No. patients Cohort/Control</th>
<th>GDM prevalence</th>
<th>Results Cohort/Control</th>
<th>P value or adjusted OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joffe, 1998, USA [56]</td>
<td>Cohort nulliparous women Prospective Multicentre</td>
<td>2-stage screening NDDG criteria</td>
<td>813/381</td>
<td>Adjustment for centre Prevalence 2%</td>
<td>GH 24.7 vs. 17.3% PE 1.4 vs. 7.1% All hypertensive diseases 37 vs. 25%</td>
<td>NS (1.28-2.11)</td>
</tr>
<tr>
<td>Ros, 1998, Sweden [57]</td>
<td>Retrospective Population of nulliparous women from a national birth registry Single centre</td>
<td>Undefined According to CIM-9</td>
<td>77/10 535</td>
<td>Adjustment for tobacco use, ethnicity, twin pregnancy</td>
<td>GH 5.2 vs. 4.4% PE 14.3 vs. 5.1%</td>
<td>NS (3.11-6.60)</td>
</tr>
<tr>
<td>Conde-Aguedelo, 2000, Uruguay [58]</td>
<td>Retrospective Latino-American and Caribbean population from an international perinatal database Multicentre</td>
<td>Undefined According to CIM-10</td>
<td>42530 PE/878 680 non PE</td>
<td>GDM with PE 17% GDM without PE 0.6%</td>
<td>RR 1.93 (1.66-2.25)</td>
<td>After multivariate analysis</td>
</tr>
<tr>
<td>Vambergue, 2002, France [59]</td>
<td>Case-control Prospective Multicentre</td>
<td>2-stage universal screening Carpenter-Coustan criteria</td>
<td>218/108</td>
<td>Exclusion of CH Adjusted for age, primiparity, BMI &gt; 27, ATCD PE</td>
<td>Gestational hypertensive complications (PE et GH) GH 14.2 vs. 4.6% PE 2.8 vs. 0%</td>
<td>2.86 (1.25-7.83)</td>
</tr>
<tr>
<td>Bryson, 2003, USA [60]</td>
<td>Retrospective Population from a birth registry Multicentre</td>
<td>Undefined According to CIM-10</td>
<td>GH (8 943) Moderate PE (5 468) Severe PE (1 180) Eclampsia (154) Controls (47 237)</td>
<td>Association with GDM Adjusted for age, ethnicity, BMI parity and level of care</td>
<td>1.40 (1.23-1.58) 1.50 (1.28-1.76) 1.53 (1.13-2.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Kvetny, 2003, Denmark [61]</td>
<td>Case-control Prospective Single centre</td>
<td>Selective Screening 75 g OGTT WHO criteria</td>
<td>89/126</td>
<td>GH 28 vs. 10% PE 4.5 vs. 1.6%</td>
<td>P = 0.003</td>
<td>NS</td>
</tr>
<tr>
<td>Ostlund, 2004, Sweden [62]</td>
<td>Retrospective Population from a national birth registry Multicentre</td>
<td>According to CIM-9 Selective screening 75 g OGTT Criteria: FG &lt; 1.20 g/L and G at 2 h &gt; 1.64 g/L</td>
<td>3 448/427 404 Prevalence DG 0.8% Prevalence PE 2.9%</td>
<td>PE 6.1 vs. 2.8% Adjusted for age, ethnicity, BMI, parity, tobacco use, CH and ATCD renal disease</td>
<td>1.61 (1.39-1.86)</td>
<td></td>
</tr>
</tbody>
</table>

associated with GDM (degree of severity, term of onset). A OR for moderate and severe preeclampsia were, respectively, 10,525 cases of GDM with a control population, the adjusted hyperglycaemia [62]. In a Swedish registry study comparing severe preeclampsia did not vary with the degree of maternal study, GDM was equally associated with severe or moderate WG (3.3%, CI 95% [2.6-3.6]) [73]. In an American population times higher in cases of preeclampsia with onset before 27 Norwegian population study found a prevalence of GDM three African American and an insufficient level of care factors (age, ethnicity, parity, weight, glycaemic balance) [66] (EL4).

Independent of insulin resistance incriminated in the pathogenesis of preeclampsia [67, 68], there could be functional abnormalities of the vascular endothelium resulting from maternal hyperglycaemia and favouring the development of preeclampsia (increase in oxidative stress, alteration of vascular reactivity to vasomodulating drugs) [67, 69, 70]. This maternal endothelial dysfunction could also be due to placental abnormalities (change in perfusion and/or maturity of trophoblast villosities) brought on by hyperglycaemia and/or insulin resistance and at the origin of the release by the placenta of different vaso-active and pro-inflammatory substances [71, 72].

According to two population studies, the main risk factors of preeclampsia in cases of GDM are, after multivariate analysis, advanced age, primiparity, high BMI, the presence of hypertension or nephropathy before pregnancy, being African American and an insufficient level of care (Table 3) [60, 62] (EL4).

There is little data on the clinical forms of preeclampsia associated with GDM (degree of severity, term of onset). A Norwegian population study found a prevalence of GDM three times higher in cases of preeclampsia with onset before 27 WG (3.3%, CI 95% [2.6-3.6]) [73]. In an American population study, GDM was equally associated with severe or moderate preeclampsia [60]. In a prospective cohort study, the risk of severe preeclampsia did not vary with the degree of maternal hyperglycaemia [62]. In a Swedish registry study comparing 10,525 cases of GDM with a control population, the adjusted OR for moderate and severe preeclampsia were, respectively, 1.94 (CI 95% [1.74-2.17]) and 1.38 (CI 95% [1.13-1.69]) [32] (EL4).

6.2. Role of insulin resistance

Insulin resistance could initiate or increase a general dysfunction in the maternal vascular endothelium that is the source of clinical and biological manifestations of preeclampsia [67, 68]. Before the HAPO study results were published, numerous case-control studies had shown an association between insulin resistance markers before 20 WG and onset of preeclampsia in the 3nd trimester, without formally establishing a causal link given the number of confusion factors associated [74-77] (EL3). The HAPO study also showed that there is a positive, continuous and independent correlation of other confusion factors (BMI, fasting glycaemia) between onset of preeclampsia and an increase in peptide C between 24 and 32 WG (adjusted OR: 1.28, CI 95% [1.20-1.36]) [63] (EL2). Independent of BMI, insulin resistance brings about metabolic modifications such as increasing certain inflammation markers (Tumor Necrosis Factor-alpha, Plasminogen Activator Inhibitor 1, C-Reactive Protein), leptin and Sex Hormone Binding Globulin, that are the origin of an alteration in the vascular endothelial function that could favour onset of preeclampsia in predisposed women [67, 68, 71] (EL3). Some authors have suggested that insulin resistance present at the beginning of pregnancy could favour the development of two distinct gestational complications that have the same pathogenic mechanism: hyperglycaemia leading to GDM and an increase in systemic vascular resistance that is the source of hypertensive complications [67]. The predictive factors of preeclampsia that complicate GDM are linked more to prior vascular complications (family history of hypertension, high systemic blood pressure in the 1st trimester), whereas the implication of the severity of insulin resistance is controversial [78-80] (EL3).

6.3. GDM and GH

Given the frequent confusion between chronic hypertension, the risk of GH is controversial in cases of treated GDM, with a prevalence that varies considerably from 2.4 to 45% according to cohort studies (Tables 1 and 3). After adjusting for the main confusion factors (age, parity, ethnicity, history of hypertension and BMI), some retrospective cohort studies found a positive, significant and independent link between GH and GDM [26, 32, 60, 61], whereas for others no association was found [56, 57, 59, 81] (EL4). In a multivariate analysis, the increase in the risk for GH was independently correlated with maternal age over 35 years, primiparity, history of preeclampsia and prior obesity [56, 59] (EL3). The ACHOIS study showed a significant decrease in GH in cases of intensive treatment of GDM compared to a control group (12 versus 18%, p = 0.02) [39] (EL1).
7. GDM and other pregnancy complications

Aside from hypertensive diseases, there is little data on the risks of gestational complications linked to GDM.

7.1. GDM and prematurity

The HAPO study showed a significant and continuous link between the risk of preterm birth and an increase in glycaemia 1 and 2 hours after administering glucose [12] (EL2). The increase in risk is nevertheless moderate (respective adjusted OR: 1.18; CI 95% [1.12-1.25] and 1.16; CI 95% [1.10-1.23]). In the randomized trial by Landon et al., the overall rate of prematurity was the same in treatment and control groups in cases of moderate GDM [40] (EL1). Increased risks in preeclampsia in cases of GDM could partially explain the increase in induced prematurity. There may be an increased risk of spontaneous prematurity, independent of obesity and other confusion factors.

An American retrospective cohort study showed a significant link between the risk of spontaneous prematurity and different degrees of maternal hyperglycaemia (positive screening test and negative OGTT, positive OGTT according to the Carpenter-Coustan or NDDG criteria) after adjusting for confusion factors [82] (EL4). Another Danish retrospective cohort study also found a significant association after multivariate analysis between spontaneous prematurity and GDM, defined as glycaemia > 2 g/L 2 hours after a 75 g dose of glucose [33] (EL4).

Two other cohort studies observed a significant increase in the premature rupture of membranes before and after 37 WG in cases of GDM [16, 23] (EL4).

7.2. GDM and risk of infection

Hyperglycaemia is classically associated with a risk of infection; very little data has evaluated this risk.

In an Israeli population study evaluating the risk factors of asymptomatic bacteriuria during pregnancy, diabetes in the larger sense (pre-existing GDM) was positively and independently associated with the risk factors [83] (EL4). Inversely, a case-control study found no increase in urinary infection risk among 149 cases of GDM, compared to 298 controls (prevalence of asymptomatic bacteriuria = 4.2%), or in risks of maternal and perinatal complications [84] (EL3). Nevertheless, it seems reasonable to consider systematic and monthly screening for asymptomatic bacteriuria in any woman with GDM [85].

Overall, there is a significant albeit modest link between the risk of preterm birth and an increase in glycaemia (EL2). GDM could increase the risk of spontaneous prematurity (EL4). However, data is still insufficient to explain this increased risk and consider preventative measures.

No recommendations can be made for the risk of infection and its prevention in cases of GDM, aside from systematic monthly screening for asymptomatic bacteriuria by using urinalysis strips (professional consensus).

8. GDM and giving birth

Diagnosing GDM according to the Carpenter-Coustan or NDDG criteria and treating it are the source of an increase in obstetrical interventions (inducing labour and Caesarean section) compared to a control population with normal glycaemia, independent of birth weight [86] (EL3).

The risk for birth complications (dystocia during labour, prolongation of the 2nd phase of labour, operative vaginal delivery, severe perineal tears and post partum haemorrhage) are all correlated with macrosomia, defined as birth weight over 4,000 g, and a risk factor independent of traumatic birth [87, 88] (EL3).

8.1. GDM and risk of Caesarean section

The HAPO study showed a linear continuous link between the rate of Caesarean section and maternal glycaemia, fasting or at 1 or 2 hours after a 75 g dose of glucose [12] (EL2). The overall rate of Caesarean section was variable from one centre to another (8.6 to 23.5%), indicating different obstetrical practices.

In most cohort studies, there is a significant increase in Caesarean rates in cases of treated or untreated GDM, compared to control groups (Tables 1 and 2). Overall rates vary greatly, between 13 and 35%, depending on the population and diagnostic
criteria. Treatment of GDM does not seem to have an influence on the risk of Caesarean section [86] (EL3). The case-control study by Langer et al. reported overall rates of Caesarean section to be identical in treated and untreated GDM groups, 24 and 23%, respectively, compared to 14% in the control group (respective OR: 1.88, CI 95% [1.45-2.43] and 1.82, CI 95% [1.47-2.27]) [18] (EL4). Two meta-analyses did not observe any difference in the overall rate of Caesarean section between treatment and control groups. (Table 2) [41, 42] (EL1).

For indications for Caesarean sections performed before and during labour, results are discordant among cohort studies, probably due to different methodologies. In cases of untreated GDM, some have observed a significant increase in the number of Caesarean sections performed during labour, most often for dystocia (abnormal progression of labour) [17, 20, 27, 28, 30] whereas others did not observe this, either with treated or untreated GDM [15, 24, 26, 86] (EL3). The statistical power of these series was often limited. In the randomized ACHOIS study, the rate of Caesarean section before and during labour was the same in the treated and control groups (15 and 12%, respectively, for Caesarean sections before labour and 16 and 20%, respectively, for those performed during labour) [39] (EL1).

The risk of Caesarean section is influenced by several confusion factors. Obesity and fetal macrosomia are risk factors independent of Caesarean section with a linear and continuous increase in rates according to maternal BMI and the baby’s birth weight [47, 87-89] (EL3).

In a case-control study, women with high BMI had an increased rate of Caesarean section when GDM was not treated compared to those of normal BMI (28 versus 19%, p < 0.01), whereas the rate was similar no matter what maternal weight was when treated [18] (EL4).

A Canadian prospective cohort study evaluated the link between birth weight and delivery method in 143 women with treated GDM and defined according to the NDDG criteria, 115 women with untreated GDM and defined only by the positive Carpenter-Coustan criteria and a control group of 3,520 women with normal glycaemia [86]. In the untreated GDM group, there were rates of macrosomia and Caesarean section significantly higher than in the control group (respectively, 28.7 versus 13.7%, p < 0.001 and 29.6 versus 20.2%, p = 0.02). In the treated GDM group, although rates of macrosomia did not increase compared to the control group, the Caesarean rate remained high (33%, OR: 2.1, CI 95%, [1.3-3.6]) after adjusting for age, ethnicity, parity, BMI, history of Caesarean, preeclampsia, birth term and birth weight. As for indications, in both treated and untreated GDM, there was an increase in the number of Caesarean sections performed before labour compared to the control group (p = 0.002). However, rates of Caesarean sections performed during labour for dystocia or fetal heart rate abnormalities were similar in both groups [86] (EL3).

The diagnosis of GDM probably has an impact on the decision for Caesarean section, which is even more often performed in cases of prenatal suspicion of macrosomia, to prevent the risk of shoulder dystocia [90-93] (EL2).

Inducing labour also seems to be a risk factor independent of Caesarean section in cases of GDM (OR: 1.8 CI 95% [1.6-2.2]) [89] (EL4). In cases of scarred uterus, and after adjusting for confusion factors, the factors associated with failure of vaginal delivery and uterine rupture were macrosomia and no prior history of vaginal route delivery [94]. In a retrospective series, the rates of success in attempting vaginal birth in cases of GDM were significantly decreased compared to a control group [95] (EL4). In another series, the presence of GDM was a risk factor independent of vaginal birth failure in cases of scarred uterus [96] (EL4). In two other cohorts, the chances of success in attempting vaginal delivery decreased with the severity of GDM, without increasing rates of maternal complications during labour (uterine rupture, hysterectomy, transfusion, maternal death) compared to a control group after adjusting for gestational age and induced labour [97, 98] (EL3).

8.2. GDM and dystocic labour

The criteria defining dystocic labour (abnormal progression of labour) have not often been evaluated in cohort studies. An Israeli cohort study observed an increased risk of dystocia during the 1st and 2nd phases of labour in cases of GDM (respective OR: 1.8, CI 95% [1.6-2] and 1.2, CI 95% [1.1-1.4]) [30] (EL4). Data is very insufficient for risks of dystocic labour, so much so that no recommendation can be made for how to proceed during labour in patients with GDM.

9. GDM and operative vaginal delivery

Macrosomia is a risk factor for operative vaginal delivery [88] (EL3). The association of operative vaginal delivery with GDM has not been evaluated much. Most cohort studies on treated or untreated GDM did not find an increase in rates of operative vaginal deliveries (Table 1) (EL4). In a Canadian prospective cohort study, rates of operative vaginal deliveries were not modified by glycaemic balance and birth weight (20 to 27%) [86] (EL3). A journal compiled a randomized study and four observational studies evaluating the benefits of inducing labour in cases of diabetes (GDM and pre-existing diabetes) compared to not inducing labour and did not find an increase in rates of operative vaginal deliveries whatever the therapeutic methods used [93] (EL2). It could be hypothesized that the absence of modification of the number of operative vaginal deliveries could be possibly linked to an increase in the number of Caesarean sections performed in cases of GDM and the fact that practitioners avoid considering operative vaginal delivery in cases of GDM, especially when macrosomia is suspected.

Macrosomia is also a risk factor independent of operative vaginal delivery failure (vacuum or forceps) [99, 100] (EL4). In an American population study, GDM was also a risk factor in failure after adjusting for macrosomia (OR: 1.54 CI 95% 1.13-2.10)
In another population study taken from Dutch birth registries evaluating risk factors in halted progression during expulsion justifying operative vaginal or Caesarean delivery, maternal diabetes (GDM or pre-existing diabetes) was a risk factor that remained after multivariate analysis in primiparous women (OR: 1.89; CI 95% 1.63-2.19) [101] (EL4). GDM could therefore be associated with a risk in operative vaginal delivery failure, especially in cases of macrosomia (EL4).

9.1. GDM and obstetric trauma

Macrosomia is a risk factor independent of severe perineal lesions (3rd and 4th degree) [88, 102, 103] (EL3). In cases of GDM associated or not with macrosomia, perineal risk has not often been evaluated. A population study from Californian birth registries found that maternal diabetes (including GDM and pre-existing diabetes) was a risk factor for anal sphincter lesions in a multivariate analysis (OR: 1.24 CI 95% 1.14-1.36) [102] (EL3). In a retrospective cohort study evaluating the risk factors for severe perineal tears, maternal diabetes was no longer associated with risk after adjusting for confusion factors [103] (EL4). Three cohort studies evaluated the criterion of perineal tears in a wider sense among patients with treated or untreated GDM [15, 21, 86]. Only one of them found a significant increase in the rate of perineal tears compared to a control group (18 versus 11%, p < 0.001) [21] (EL4). Despite a significant decrease in macromomic newborns, the ACHOIS trial did not find any benefits from GDM treatment for perineal risk, with rates of perineal tears identical in both treatment and control groups [39] (EL1).

9.2. GDM and post partum haemorrhage

After multivariate analysis, macrosomia, inducing labour, Caesarean section and preeclampsia were found to be risk factors independent of post partum haemorrhage [87, 88, 104, 105] (EL3). This judgment criterion has not been highly evaluated in treated and untreated GDM. According to the ACHOIS trial, the risk of post partum haemorrhage was not modified with treatment of GDM, despite a significant increase in the number of induced labours [39] (EL1).

Overall treated or untreated GDM is associated with an increase in the risk for Caesarean delivery, independent of birth weight (EL2). Obesity and macrosomia are risk factors independent of Caesarean delivery (EL3). In cases of GDM, prenatal suspicion of macrosomia is a risk factor for Caesarean delivery (EL3). GDM also influences the prognosis of attempted vaginal birth in cases of scarred uterus (EL3).

GDM is not associated with an increase in the risk for operative vaginal delivery (EL3), perineal tears (EL2) and post partum haemorrhage (EL2).

10. GDM and post partum complications

Post partum complications linked to the presence of GDM have scarcely been evaluated. The ACHOIS study found identical risks of puerperal fever and hospital stay durations between treatment and control groups [39] (EL1).

10.1. Risks linked to obesity

Obesity is responsible for a significant increase in certain post partum complications, especially after Caesarean delivery (urinary infection, haematoma and infection of the uterine walls, endometriosis, hernia and venous thrombosis) [43, 106] (EL3). There is little data on its association with GDM on specific post partum risks. An Israeli population study evaluated the risk factors for uterine wall infection onset among 19,416 Caesarean cases (3.7% of patients) [107]. Multivariate analysis found as independent risk factors: obesity (OR: 2.2; CI 95% [1.6-3.1]), diabetes (GDM and pre-existing diabetes, OR: 1.4; CI 95% [1.1-1.7]), hypertensive disease (OR: 1.7; CI 95% [1.4-2.1]), premature rupture of membranes (OR: 1.5; CI 95% [1.2-1.9]) and emergency Caesarean delivery (OR: 1.1; CI 95% [1.1-1.5]); the association of obesity and diabetes increased risk (OR: 9.3; CI 95% [4.5-19.2]) [107] (EL4).

10.2. GDM and post partum thrombotic risk

In a Norwegian population study, GDM was a risk factor for prenatal venous thromboembolic accidents after a multivariate analysis, not accounting for BMI (OR: 4.1 CI 95% 2.0-8.9) [108] (EL4). GDM was not retained as a clinical risk factor by learned societies that gave recommendations for clinical practices on obstetrical prevention of venous thromboembolic disease [109-112]. Whatever the case, GDM is often associated with high risk situations requiring thromboprophylaxis during the post partum period (Caesarean section, preeclampsia, obesity, age over 35 years).

Overall, GDM associated with obesity requires extreme vigilance in terms of preventing post partum complications (EL4).

Thrombotic risk in cases of GDM is linked to associated clinical risk factors (Caesarean, preeclampsia, obesity, age over 35) (professional consensus).

11. GDM and psychological problems

A diagnosis of GDM can have a negative psychological impact since the risks for mother and child and medical care with various therapeutic constraints must be elicited.

After an Australian prospective cohort study (n = 209), diagnosing GDM between 24 and 28 WG was the source of a significant change in perception by diabetic women of
the quality of their health [113]. However, the perception of their child’s health, as well as scores evaluating anxiety and depression, were not modified compared to non diabetic women, be it at the time of screening or at 36 WG (EL3). Another Australian longitudinal prospective study (n = 100) found anxiety scores significantly higher at the beginning of treatment for GDM but they then became comparable to those in the control group at 36 WG or 6 weeks post partum [114] (EL3).

The psychological impact of intensive treatment of GDM was evaluated in the randomized ACHOIS study via scores on quality of life, anxiety and depression questionnaires addressed to 916 patients at 6 weeks after diagnosis and 3 months post partum [39]. In the treatment group there was a significant decrease in the risk of depression at 3 months post partum (adjusted RR: 0.46; CI 95% [0.29-0.73]). Risks for anxiety were similar in both groups at 6 weeks after diagnosis and at 3 months post partum. However, several score criteria for quality of life were significantly better in the treatment group [39] (EL1).

Overall, psychological problems such as anxiety that modify self-perception can be present at the time of diagnosis of GDM (EL3). GDM treatment decreases the risk of post partum depression (EL2).

12. Conflicts of interest
No conflicts related to the article

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