Outcomes in women with a history of gestational diabetes. Screening and prevention of type 2 diabetes. Literature review

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Abstract

Women with a history of gestational diabetes mellitus (GDM) are characterized by a high risk of type 2 diabetes mellitus (T2DM) (x 7), metabolic syndrome (x 2 to 5) and cardiovascular diseases (x 1.7). Women with lesser degrees of glucose intolerance share the same risks. T2DM may occur from post-partum (5 to 14%) to several years later, up to 25 years. Some factors associated with T2DM are identified: obesity, early diagnosis of GDM before 24 weeks gestation, high pregnancy OGTT blood glucose or insulin-therapy during GDM. Screening for T2DM only with fasting glucose provides less sensitivity than with OGTT; HbA1c may supplant these dosages. The recurrence rate of GDM is between 30 and 84%, non-white ethnicity and insulinotherapy during GDM being the best proven predictors. High risk women need repeated life-long screenings for glycaemic abnormalities, or when another pregnancy is planned.

Among obese women with history of GDM who show minor glycoregulation disturbances, modifications of lifestyle in intensive programs or metformin halve the risk of DT2. However, studies analysing practices show low adhesion to screening; without an intensive program, few women implement lifestyle modifications. These intensive programs should be implemented and proposed to high-risk women. Their therapeutic education should also include prevention of cardiovascular risk factors.

Keywords: gestational diabetes mellitus, screening, type 2 diabetes, cardiovascular disease, metabolic syndrome, review

Résumé


Un antécédent de diabète gestationnel (DG) augmente le risque de diabète de type 2 (DT2 (x 7), de syndrome métabolique (x 2 à 5) et de maladies cardiovasculaires (x 1.7) ; un trouble moindre expose aux mêmes pathologies. Le DT2 peut apparaître dès le post-partum (5 à 14 % des cas) ou plus tard (sur-risque jusqu’à 25 ans). Les facteurs associés au DT2 sont l’obésité, l’apparition du DG avant 24 semaines, des glycémies élevées lors du diagnostic ou la nécessité d’une insulinothérapie lors du DG. Le dépistage par la glycémie à jeun offre moins de sensibilité que l’HGPO : l’HbA1c pourrait supplanter ces dosages. La récurrence du DG est de 30 à 84 %, plus fréquente chez les non-caucasiennes ou en cas de DG insulinotraitée. La surveillance du statut glycémique doit être poursuivie chez les femmes à risque ou si une autre grossesse est prévue. Chez les femmes présentant après le DG des troubles mineurs de la glycorégulation et obèses, il est prouvé que les modifications intensives du mode de vie ou la metformine diminuent de moitié le risque de DT2. L’adhésion au dépistage reste faible. Peu de femmes modifient leur mode de vie sans programme d’accompagnement, qui doivent donc être mis en place et proposés aux femmes les plus à risque. Leur éducation thérapeutique portera aussi sur la prévention des facteurs de risque cardio-vasculaires.

Mots clés : diabète gestationnel, dépistage, diabète de type 2, pathologie cardiovasculaires, syndrome métabolique, revue
Abundant literature has established the relationship between gestational diabetes (GDM) and type 2 diabetes (T2DM) (beta-cell dysfunction) [1-2]. Long-term metabolic complications are therefore expected.

1. Methods

Systematic literature reviews were carried out in the PubMed and Cochrane databases using all data since their inception up to 21 May 2010 and various key words. Articles published in English, relating to women and with original data were retained. These first lists were then enriched by searches in the bibliographic references of the articles retained.

To study the incidence of T2DM after GDM, the key words «diabetes mellitus», «type 2 diabetes mellitus», «NIDDM», «non insulin dependent diabetes mellitus», «after», «gestational diabetes», «diabetic pregnancy» helped in the selection of 145 articles. Among these, we looked for recent meta-analyses (since 2000), studies of clinical incidence prior to the date of the last meta-analysis [3], i.e. after 31 Jan 2009; the last systematic review of studies of very early incidence and articles published since then; studies of very delayed incidence (longer than 25 years).

To study the incidence of metabolic syndrome after GDM, the search was carried out with the following keywords: “metabolic syndrome X” “and” “gestational diabetes”, it resulted in the selection of 53 articles. The 25 articles relating to clinical studies of the incidence of metabolic syndrome or of maternal cardio-vascular risk factors after GDM were retained.

To study the incidence of cardiovascular diseases after GDM, the keywords “cardiovascular disease”, “after” and “gestational diabetes” were used to select 178 articles. We retained the 6 articles relating to clinical studies of the incidence of maternal cardio-vascular diseases after GDM.

<table>
<thead>
<tr>
<th>Author Country</th>
<th>Study type Year</th>
<th>Ethnic origin</th>
<th>Mean maternal age (years, SD) of women with GDM / Non-GDM</th>
<th>GDM criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogonowski 2009  Poland [7]</td>
<td>Prospective cohort 2005-2007</td>
<td>Caucasian</td>
<td>30.96 (0.29)</td>
<td>WHO 1999</td>
</tr>
<tr>
<td>Schaefer-Graf 2009 Germany [8]</td>
<td>Multicentric prospective cohort 2000-2005</td>
<td>Mixed</td>
<td>32.7 (4.5)</td>
<td>ADA 75 g</td>
</tr>
</tbody>
</table>
Finally, for the incidence of type 1 diabetes (T1DM) after GDM, the keywords “type 1 diabetes mellitus”, “after” and “gestational diabetes” were used to select 138 articles, of which 13 were retained relating to clinical studies of the incidence of maternal T1DM after GDM.

2. Incidence of diseases observed after GDM

2.1. Incidence of T2DM after GDM

2.1.1. Systematic reviews and meta-analyses

A systematic review with meta-analysis was recently published by Bellamy et al. [3]. The inclusion criteria (retrospective or prospective study with a control group and excluding patients with known T1DM or T2DM, tested at least six weeks post partum) resulted in the selection of 20 cohort studies carried out between 1960 and 31 Jan 2009. Among the 675,455 women studied, 10,859 presented with T2DM. The relative risk (RR) of T2DM was 7.43 (CI [4.79-11.51]). Less than 5 years after GDM RR was 4.69 (CI [2.84-7.75]); beyond that RR was 9.34 (CI [3.42-25.54]).

Adjustments were made for ethnicity, age, body mass index (BMI) and survival duration. The relative risk was coherent between the various studies. The relationship remained whatever the GDM or diabetes criteria used. The largest cohort, represented by the Ontario data (n = 659,164; 9,502 T2DM) had the highest RR: 12.6 (CI [12.15-13.19]) [4]. Complete follow-up was 100% in nine studies, 96% in the largest study [4], 44% in the second largest and greater than 70% in five others; elsewhere it was not indicated.

No stratification was possible on family history of diabetes or personal history of GDM.

A previous systematic review of 28 studies was published by Kim et al. in 2002 [5], but concerned few Caucasian populations. There was no systematic control group, and generalisation of results was made difficult by study heterogeneity. Nevertheless, it indicated that T2DM appeared rapidly within the first 5 years and plateaued-off after 10 years.

The population attributable risk for GDM was evaluated by Cheung et al. [6] in a meta-analysis of 6 observational studies, with control groups, of the progression of GDM to T2DM. The RR of developing T2DM was 6.0 CI [4.1-8.8]. Based on a literature review of studies of prevalence between 1992 and 2002, the authors calculated that the population attributable risk for the general population ranged from 0.10 to 0.31. This indicates that between 10 and 31% of barouf women with diabetes would have experienced a GDM pregnancy earlier.

2.1.2. Results of studies published after the meta-analysis by Bellamy et al. (> 31 Jan 2009) [3]

This studies had no control groups [7-10] (Table 1) and therefore do not correspond to the inclusion criteria for the meta-analysis by Bellamy et al. [3]. The incidence is coherent with the increased risk highlighted of Bellamy et al.’s review [3]. The British population in the study by Kakad et al. [10] included almost 30% obese patients, which explains the higher incidence level.

We would like to indicate a particular study of incidence in a high-risk population for T2DM, in the American prospective study “Diabetes Prevention Program” (DPP) [11]. Patients included in the DPP needed to have already a moderate glucose tolerance disorder, defined as moderate fasting hyperglycaemia (MFG) (between 0.96 and 1.26 g/L, or 5.2 and 7 mmol/L) and simultaneous glucose intolerance (I) (glycaemia at 2 hours OGTT ≥ 1.4 g/L (7.7 mmol/L) and < 2 g/L (11 mmol/L). The randomized, controlled DPP study contained 3 arms; one arm with placebo and standard intervention (twice yearly

<table>
<thead>
<tr>
<th>Total number of women studied</th>
<th>Mean follow-up (SD)</th>
<th>Definition of T2DM</th>
<th>% T2DM</th>
<th>% intol</th>
<th>% MFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>318</td>
<td>6 (5-9) weeks</td>
<td>WHO</td>
<td>1.3%</td>
<td>7.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>605</td>
<td>13 weeks</td>
<td>WHO</td>
<td>5.5%</td>
<td>13.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>5857</td>
<td>1 to 26 weeks</td>
<td>ADA</td>
<td>1.1%</td>
<td>16.3% (intol and MFH)</td>
<td>16.3% (intol and MFH)</td>
</tr>
<tr>
<td>470</td>
<td>1 year</td>
<td>WHO</td>
<td>8.1%</td>
<td>14.9%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

lifestyle advice), the other two arms being intensive life style modifications or metformin.

Women in the placebo arm, with (n =122) or without a history of GDM (n = 487) (self-declared), constitute the population for the study of the incidence of T2DM; patients having rapidly developed T2DM post partum or having had a stillbirth were excluded. The average age of women with a history of GDM was 43 (versus 52); their BMI was high (GDM: 34.2 ± 6.2 versus 34.6 ± 6.8) and 55% were Caucasian. Incidence, adjusted for age, was 15.2 per 100 person-years in cases of GDM, versus 8.9 in the non-GDM population (p < 0.05), on average 12 years after GDM[11]. The authors concluded that progression to T2DM was more common after GDM, despite equivalent degrees of impaired glucose tolerance at baseline.

2.1.3. Precocity

T2DM can appear within the first weeks post partum. Early persistence of glucose anomalies hints at a pre-existing unrecognized disorder.

A literature review of observational studies since 1998 carried out by Kitzmiller et al. in 2007 [12] in women whose GDM was managed showed that, globally, between 4 and 20 weeks after giving birth, the prevalence of T2DM was between 5 and 14%. That of IGT was between 7 and 29%, while that of fasting hyperglycaemia was between 3 and 6%. Kitzmiller et al. observed that prevalence seemed to vary depending on the rate of obesity in the population and on criteria for diagnosing GDM, but irrespective of geographic localisation.

Incidence of early post partum T2DM from the most recent studies [7-9] was at the lower end of these ranges (Table 1). The lower incidences of Lawrence et al. [10], between 1 and 26 weeks after giving birth, were probably under-estimated, as 79% were tested using only fasting glycaemia.

2.1.4. The increased risk of glucose tolerance disorders after GDM extends over a long period

The increased risk after GDM persisted for 15 years in the study by Linné et al. [13], 20 years in the study by Gunderson et al. [14], and up to 28 years in the longest follow-up to date, with the historical O’Sullivan et al. cohort [15]. Beyond this time there is no data, but the risk is not expected to disappear. In addition, it is known that ageing alone is a risk factor for T2DM.

2.1.5. The risk of incidence of T2DM after GDM seems to be increasing in recent cohorts

Two Danish cohorts [16] of women treated by diet alone were compared; in the older patients were recruited between 1978 and 1985 (n = 151) and patients in the newer study between 1987 and 1996 (n = 330). After a median follow-up of 9.8 years, the level of T1DM and T2DM was 18% in the older cohort and 40.9% in the newer one; identical methods were used. The BMI of the second cohort was higher (26.0 [22.5-30.8] versus 22.9 [20.2-28] (p < 0.0005)). A BMI greater than 25 was an independent predictor of T2DM. The authors concluded that this increase could appear to be linked to increased obesity.

2.1.6. What about in France?

The only French study was based in the Nord-Pas de Calais region (Diagest 2) [17]. In this prospective study of Caucasian women (included in the meta-analysis by Bellamy et al. [3]), 39.9% of GDM patients were shown to have anomalies of glucose tolerance (T2DM: 18%, IGT: 13.4% and MFH: 8.5%) versus 6.3% (0.9%, 2.1% and 3.6%, respectively) among controls over the course of a 6.7 year follow-up.

Obesity rate in this region in 1997 was 13.5%, close to the current national levels (14.5%) (OBEPI-Roche survey 2009) [18]. However, it is not possible to extrapolate these regional results to the whole of France.

2.1.7. Patients with mild hyperglycemia problems during pregnancy also have an increased incidence of T2DM

These studies [17,19-21] are summarized in Table 2. Globally, the incidences of T2DM, IGT or MFH after GDM are two or three times higher compared to a control group.

Conclusion

A history of GDM significantly increases the future risk of T2DM, which is multiplied by 7 (within the 5 years following GDM, by 4.7; after that by 9.3) (PL2).

Mild hyperglycemia below diagnostic of GDM, also increases the risk of developing T2DM by a factor of 2 to 3 (PL2).

2.2. Metabolic syndrome (MS) after GDM

MS is a combination of a number of cardiovascular risk factors. Because of evolutions in disease classification, the number varies depending on the definition used. It predicts an increased risk of cardiovascular diseases and also of T2DM.

The definition according to the National Cholesterol Adult Treatment Panel III [22] requires three of the following five elements: waist measurement > 88 cm, fasting triglycerides (TG) ≥ 1.5 g/L (1.7 mmol/L) or treatment for hypertriglyceridemia, HDL cholesterol < 50 mg/L (1.29 mmol/L) or treatment for
HDL hypocholesterolemia, blood pressure ≥ 130 or ≥ 85 mmHg or treatment for hypertension, fasting glycaemia ≥ 1 g/L (5.6 mmol/L) or treatment for diabetes. The current IDF definition [23] for women includes the following criteria: abdominal circumference greater than 80 cm in combination with 2 of the following: hyperglycaemia, hypertension, dyslipidaemia. All these parameters are defined as above.

Studies [24-43] are summarised in Table 3.

Sixteen studies [24, 26, 27, 30-35, 37-43] out of the 20 examined indicate a 2 – to 5-fold increase in incidence of MS after GDM. For example, in the Danish cohort study by Lauenborg et al. [26], 10 years after GDM the incidence of MS was 36%, compared to 13% in the control population. Kousta et al. [31] showed that Caucasians are less at risk of MS. MS after GDM can be diagnosed early (4 months) [43] or late (20 years) [39] in a well-followed cohort (72%).

The other four studies, in Europe [28, 29] or not [25], did not find any MS after GDM, in women of normal weight in Brazil [25]. Kim et al. [36] recruited women with a history

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study type</th>
<th>Ethnic group</th>
<th>Mean maternal age (years, SD)</th>
<th>Mild pregnancy hyperglycaemia / controls</th>
<th>Criteria of mild pregnancy hyperglycaemia</th>
<th>Total number of women studied (degree of matching mild pregnancy hyperglycaemia / controls)</th>
<th>Mean follow-up (years, SD)</th>
<th>Definition of T2DM or intolerance or MFH</th>
<th>% or relative risk of T2DM or intolerance or MFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrado</td>
<td>2007</td>
<td>Italy (Sicily)</td>
<td>Prospective cohort</td>
<td>Caucasian</td>
<td>33.7 (5.2) / 32.7 (5.2)</td>
<td>Carpenter and Coustan / 1 abnormal OGTT value</td>
<td>66 / 56 Controls matched for BMI and year of birth</td>
<td>6.6 ADA 1997</td>
<td></td>
<td>T2DM / 11 / 66: T2DM 1 / 66: intolerance 5 / 66: MFH Total: 28.7% versus 9.7% (p = 0.01)</td>
<td></td>
</tr>
<tr>
<td>Vambergue</td>
<td>2008</td>
<td>France (Nord-Pas-de-Calais)</td>
<td>Prospective cohort</td>
<td>Mixed</td>
<td>38 (6) / 37 (5.6)</td>
<td>Carpenter and Coustan / 1 abnormal OGTT value</td>
<td>175 / 111 controls</td>
<td>6.7 (0.8) ADA 1997</td>
<td></td>
<td>T2DM: 6.3% versus 0.9% (p &lt; 0.05) Intolerance: 11.3% 2.1% (p &lt; 0.05) MFH: 6.3% versus 3.6% (NS) total: 23.9% versus 6.9% (p = 0.005)</td>
<td></td>
</tr>
<tr>
<td>Carr</td>
<td>2008</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>Mixed</td>
<td>32.2 (5.7)</td>
<td>Carpenter and Coustan / 1 abnormal OGTT value</td>
<td>6,222</td>
<td>9.7 ADA 1995</td>
<td></td>
<td>T2DM HR 2.08 [CI 1.35-3.20]</td>
<td></td>
</tr>
<tr>
<td>Retnakaran</td>
<td>2009</td>
<td>Canada</td>
<td>Retrospective cohort</td>
<td>Mixed</td>
<td>34.0 (4.4) / 33.8 (4.2)</td>
<td>Carpenter and Coustan / O’Sullivan: + and 4 normal OGTT values</td>
<td>15,381</td>
<td>6.4 Canada 2003</td>
<td></td>
<td>T2DM incidence: 5.04 / 1000 patients. year versus 1.74 Hazard ratio (HR) = 2.56 [CI 2.28-2.87]</td>
<td></td>
</tr>
</tbody>
</table>
Table 3
Review of the literature: incidence of metabolic syndrome after gestational diabetes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Type of study</th>
<th>Ethnic origin</th>
<th>Mean maternal age years(SD) of women / controls</th>
<th>GDM criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimenta</td>
<td>Brasil [25]</td>
<td>Retrospective case-control study</td>
<td>Mixed</td>
<td>34.5 / 33.4</td>
<td>NDDG</td>
</tr>
<tr>
<td>Lauenborg</td>
<td>Denmark [26]</td>
<td>Prospective cohort study 2000-2002</td>
<td>Mixed</td>
<td>43 (inter quartile: 38-48)</td>
<td>75 g Fasting &gt; 1.13 g / L (6.2 mmol / L) 2 h &gt; 1.62 g / L (8.9 mmol / L)</td>
</tr>
<tr>
<td>Noussitou</td>
<td>Switzerland [27]</td>
<td>Retrospective study</td>
<td>Mixed</td>
<td>32.3 (0.45) / 33.6 (0.78)</td>
<td>NDDG 1979</td>
</tr>
<tr>
<td>Albareda</td>
<td>Spain [28]</td>
<td>Prospective cohort</td>
<td>Caucasian</td>
<td>30.7 / 30.4</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Di Benedetto</td>
<td>Italy [29]</td>
<td>Transversal study</td>
<td>Caucasian</td>
<td>35.6 (4.4) / 32.5 (7.8)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Lin</td>
<td>China [30]</td>
<td>Retrospective case-control study</td>
<td>Chinese</td>
<td>34.0 (4.6) / 33.8 (4.4)</td>
<td>NDDG</td>
</tr>
<tr>
<td>Kousta</td>
<td>Great Britain [31]</td>
<td>Retrospective study 1997-1999</td>
<td>Mixed</td>
<td>35.7 (35.2-36.2) / 34.8 (34.3-5.3)</td>
<td>WHO</td>
</tr>
<tr>
<td>Carr</td>
<td>USA [32]</td>
<td>Transversal study</td>
<td>Mixed</td>
<td>48.6 (0.7) / 52.4 (0.6)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Di Cianni</td>
<td>Italy [33]</td>
<td>Retrospective cohort</td>
<td>Caucasians</td>
<td>34.7 (4.2) / 33.9 (3.9)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Krishnaveni</td>
<td>Southern India [34]</td>
<td>Prospective cohort 1997-1998</td>
<td>Non Caucasian</td>
<td>(mached for age) 33.5 (29.5-38.5) / 32.2 (28.0-36.0)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Wender-Ozegowska</td>
<td>Poland [35]</td>
<td>Retrospective cohort 1993-2002</td>
<td>Caucasians</td>
<td>28.3 (6.0) / 26.5 (3.7)</td>
<td>-</td>
</tr>
<tr>
<td>Kim</td>
<td>USA [36]</td>
<td>Transversal study in the Third National Health and Nutrition Examination cohort 1988-1994</td>
<td>Mixed</td>
<td>32.2 (1.1) / 39.2 (0.2)</td>
<td>Declarative</td>
</tr>
<tr>
<td>Vohr</td>
<td>USA [37]</td>
<td>Prospective cohort</td>
<td>-</td>
<td>-</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Total number of women studied</td>
<td>Mean follow-up (SD or 95% CI)</td>
<td>Definition of metabolic syndrome</td>
<td>% or relative risk of metabolic syndrome (MS)</td>
<td></td>
<td></td>
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<td>-------------------------------</td>
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</tr>
</tbody>
</table>
| 838 GDM                      | 1-3 years                   | BMI, Waist measurement, HBP, Lipids | *BMI, waist measurement, BP, triglycerides: high  
*Total cholesterol and HDL: NS |
| 20 pairs of GDM / controls, matched for age, BMI, hip / waist ratio | Up to 12 years | BMI, Waist / hip ratio, Lipids | Lipids: NS |
| 481 GDM / 1 000 Controls matched for age | 9.8 years (6.9-17.2) Interquartile interval | WHO 1999, NECPATP III 2001, EGI 2002 | *WHO: 38.4% versus 13.4% p < 0.0005  
*ATPIII: 43.5% versus 14.8% p < 0.0005  
*EGIR: 32.4% versus 11.1% p < 0.0005 |
| 159 GDM                      | 3 years                     | Obesity, HBP, and / or dyslipidaemia | Presenting one element of MS is an independent predictor of glucose intolerance anomalies post GDM  
OR = 5.3 (CI 1.3-22.2) |
| 262 GDM / 66 controls        | 5 years                     | NCEP-ATP III 2001 | BP, waist measurement, LDL-cholesterol higher; but no increased prevalence of MS |
| 26GDM / 26 controls          | 1-3 years                   | Composite elements | Higher insulin resistance and CRP  
Lipids: NS |
| 17GDM / 73 controls, matched for age, BMI, hip / waist ratio | 3.3 months (1-19) | Composite elements | 23.5% versus 2.7%  
p<0.01 |
| 368 GDM / 482 controls       | 20 months Geometric mean (CI 18.2-22.1) | IDF | * 27% versus 10  
* Lower prevalence in Caucasians (28% p < 0.001) |
| 332 GDM / 663 controls       | -                           | NCEP-ATPIII | 86.6% versus 73.5% (p < 0.001) |
| 166 GDM / 98 controls        | 1.4 years                   | NCEP-ATP III | 9% versus 1% p < 0.001  
After regression analysis, independent correlation of CRP with HOMA-R (r2 = 0.27, p < 0.001) |
| 35 GDM / 489 controls        | 5 years                     | IDF / Southern Asia | 60% versus 26%  
(OR 4.4 [CI 2.2-8.9] p < 0.001) |
| 74 GDM / 155 controls        | 6.0 (2.7) / 5.1 (2.7) years | NCEP-ATP III 2005 criteria | 30.7% versus 5.2% controls  
(p < 0.001) |
| 85 GDM / 4,328 controls      | -                           | NECP-ATP III | NS |
| 56 GDM / 48 controls         | 11 years                    | NECP-ATP III | Risk x 4.4  
([CI 1.7-11.1] p = 0.002) |
of GDM (n = 85) from the «National Health and Nutrition Survey» cohort and compared them to those with no history of GDM (n = 4,328). There were no differences between them, but the abnormally low rate of GDM may be the result of a bias (only women in good health participated).

In older studies on cardiovascular risk factors after GDM [44-48], which are not included in Table 3, no MS was discovered, but higher lipid levels were present.

Anomalies relating to indirect markers of MS, which are beyond the scope of this review, have also been reported [49, 50], in line with the underlying physiopathology.

2.3. Conclusion

A history of GDM increases the risk of metabolic syndrome (by 2 – to 5-fold) (EL2).

2.4. Incidence of cardiovascular diseases after GDM

Table 4 summarises the studies of incidences found in the literature [51-56]. Overall, the risk is increased by about 1.7-fold.

A retrospective Canadian cohort from an administrative database was analysed in two recent publications. Firstly, Shah et al. in 2008 [54] showed that the incidence of cardiovascular events increased 11.5 years after GDM (n = 8,191 GDM and 81,262 controls) (hazard ratio (HR) 1.71 [CI 1.08-2.69]).

Then, in 2009, Retnakaran et al. [55] confirmed this risk 12.3 years after GDM (n = 13,888 GDM, control group with normal glycaemic tolerance: n = 349,977). After adjustment for: age, year of giving birth, place of residence, revenue, comorbidities and pre-existing or gestational hypertension, the HR compared to the control population was 1.6 (CI 1.3-2.13) (p < 0.001). In addition, the same analysis was carried out in positive and normal OGTT O’Sullivan’s screening test groups, i.e. minimal glycoregulation problems (n = 71,831); after 12.6 years (n = 39,555) their risk had increased slightly (HR 1.19 [CI 1.02 -1.39]) (p = 0.03). This corresponds to a non GDM group, so is not reported in Table 4.

Dawson et al. [56] reported a prospective cohort study without a control group: 753 women followed over 20 years. After adjustment for age, BMI and tobacco use, patients in the highest quartile for pregnancy HbA1c (but below the level diagnosing diabetes) had significantly more events.

Two studies [51, 53] found cardiac neurovegetative dysautonomy (cardiac variability), which is an independent marker of cardiovascular death.

### Table 4

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Type of study</th>
<th>Year</th>
<th>Ethnic origin</th>
<th>Mean maternal age years (SD) of women / controls</th>
<th>GDM criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivero</td>
<td>Brazil</td>
<td>Prospective cohort followed from 1999 to 2003</td>
<td>2008</td>
<td>Mixed</td>
<td>35.6 (6.6)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Gunderson</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>2007</td>
<td>Mixed</td>
<td>Paired for age</td>
<td>Local</td>
</tr>
<tr>
<td>Madarasz</td>
<td>Hungary</td>
<td>Retrospective cohort</td>
<td>2009</td>
<td>Caucasian</td>
<td>36.1 (6) / 33.6 (5.9)</td>
<td>WHO 1985</td>
</tr>
<tr>
<td>Maghbooli</td>
<td>Iran</td>
<td>Case-control study</td>
<td>2010</td>
<td>Iranian</td>
<td>32.5 (5.2) / 27.9 (7.0)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Akinci</td>
<td>Turkey</td>
<td>Retrospective cohort</td>
<td>2010</td>
<td>Turkish</td>
<td>33.6 (4.5) / 33.5 (4.5)</td>
<td>Carpenter and Coustan</td>
</tr>
<tr>
<td>Retnakaran</td>
<td>Canada</td>
<td>Prospective cohort</td>
<td>2010</td>
<td>Mixed</td>
<td>34.5 (4.3) / 33.9 (4.3)</td>
<td>Carpenter and Coustan</td>
</tr>
</tbody>
</table>

2.5. GDM recurrence

2.5.1. Who is at risk of recurrence?

Kim et al.’s systematic review [57] included 13 studies (up through the end of 2006). Depending on the country, the rate varies between 30 and 84%. The most frequently encountered predictive factor was non-white ethnic origin, although this detail was not always indicated. Levels reached 50 to 69% in “ethnic minorities” and 30 to 37% in white, non-hispanic populations. Other risk factors were sometimes found: maternal age, parity, BMI, OGTT results and need for insulin treatment. It should be noted that two studies [58, 59] showed that the probability of recurrence reached 75 to 77% if insulin treatment was required during a previous pregnancy. To our knowledge, the predictivity of insulin dose has not been studied.

2.5.2. Influence of obesity, weight variations and physical activity

The level of obesity, weight variations- even slight (5 to 10 kg) – and physical activity play a major role in primary prevention of GDM (see: Galtier F, Definitions, epidemiology, risk factors). For secondary prevention, it is probable that the same factors play a role. However, we have not found any studies proving this supposition.

2.5.3. Prevention of GDM recurrence with metformin?

Studies looking into metformin-based prevention are presented in Table 5 [60-64], only one of these [63] relates to secondary prevention. They do not allow formal conclusions to be drawn.

Conclusion
The risk of recurrence is high, between 30 and 84%; non-Caucasian women or those who received insulin during pregnancy run a higher risk (EL2).

2.6. Incidence of T1DM after GDM

It is rare for T1DM to be declared after GDM. However, in Scandinavia this happens in between 2 and 10% of women who have had GDM, which is in line with the higher incidence of T1DM in this part of the world [65-68]. In Australia the incidence was 1.7% in a prospective study (n = 734) [69].

This low risk of T1DM after GDM does not have the same incidence on public health as T2DM. However, «auto-immune» GDM [70] carries a real individual risk due to a possible evolution towards ketoacidosis. It is therefore important to detect these patients.
T1DM onset can be predicted by a high level of anti-GAD and/or ICA antibodies, early detection is easier when there are several antibody types [65, 67, 71]. They are detected in about 10% of GDM. The level varies depending on the prevalence of T1DM in the geographical area (extensively reviewed in [72, 73]). It can appear between one and 15 years later [66, 72, 73] therefore, follow-up must be long-term.

Table 4
Literature review: incidence of cardio-vascular disease after GDM.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Type of study</th>
<th>Ethnic origin</th>
<th>Mean maternal age (years, SD) of women with GDM / controls</th>
<th>GDM criteria</th>
<th>Total number of women studied (degree of matching GDM/non-GDM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerenyi</td>
<td>Hungary</td>
<td>Retrospective cohort</td>
<td>Caucasian</td>
<td>37.5(6.3)</td>
<td>WHO 1985</td>
<td>124 GDM</td>
</tr>
<tr>
<td>Carr</td>
<td>USA</td>
<td>Transversal study 1st degree family history of T2DM</td>
<td>Mixed</td>
<td>48.6 (0.7)/52.4 (0.6) P &lt; 0.001</td>
<td>Carpenter and Coustan (self-declared)</td>
<td>332 GDM/663 controls</td>
</tr>
<tr>
<td>Gasic</td>
<td>Austria</td>
<td>Retrospective cohort</td>
<td>Caucasian</td>
<td>32.8 (0.9)/33.8 (2.0)</td>
<td>IVth Workshop</td>
<td>48GDM/20 matched controls</td>
</tr>
<tr>
<td>Shah</td>
<td>Canada</td>
<td>Retrospective cohort on administrative database</td>
<td>Mixed</td>
<td>NA</td>
<td>Carpenter and Coustan</td>
<td>8,191 GDM/ matched with 10 controls</td>
</tr>
<tr>
<td>Retnakaran</td>
<td>Canada</td>
<td>Retrospective cohort (partly same as Shah et al. 2008)</td>
<td>Mixed</td>
<td>31.1/29.2</td>
<td>Carpenter and Coustan</td>
<td>13,888 GDM/349,977 controls</td>
</tr>
<tr>
<td>Dawson</td>
<td>New Zealand</td>
<td>Prospective cohort</td>
<td>Mixed</td>
<td>26.2/25.8 /26.0/25.6</td>
<td>HPIV (Fisher 1974)</td>
<td>753 GDM</td>
</tr>
</tbody>
</table>

Table 5
Studies of prevention of gestational diabetes using metformin (Met)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type, year</th>
<th>Definition</th>
<th>Comparable groups?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanky [60] and Fougner [61] Norway Prospective 2004</td>
<td>- PCOS - Met from T1</td>
<td>- PCOS - placebo</td>
<td>Yes (randomised, double-blind)</td>
</tr>
<tr>
<td>Nawaz [62] Pakistan Prospective 2008</td>
<td>- PCOS - Met pre-conception - A (Met stopped at 16 weeks LMP) - B (Met stopped at 32 weeks LMP) - C (Met continued)</td>
<td>- PCOS - No Met</td>
<td>yes</td>
</tr>
<tr>
<td>Glueck [63] USA Prospective 2008</td>
<td>- PCOS - Met preconception and throughout pregnancy</td>
<td>- PCOS - Previous pregnancy without Met in these patients</td>
<td>No: Older cases</td>
</tr>
<tr>
<td>Begum [64] Bangladesh Prospective 2009</td>
<td>- PCOS - Met at conception - Met throughout pregnancy</td>
<td>- PCOS - Met at conception - Met stopped T1</td>
<td>yes</td>
</tr>
</tbody>
</table>

Some clinical characteristics indicate a need to assay for antibodies: young age, normal weight before pregnancy, no family history of T2DM, family or personal history of autoimmune diseases (Hashimoto’s thyroiditis, vitiligo etc.) and need for transitory insulin therapy during GDM [71, 74]. However, the classical risk factors for GDM can be present with T1DM [75] and the prevalence of obesity increases them [18].
Conclusion

GDM does not increase the risk of T1DM but can reveal it (PL4).

There is no reason to systematically screen for T1DM after GDM by anti-GAD antibodies. Some clinical characteristics can indicate a need to assay anti-GAD antibodies (family or personal history of auto-immune disease, need for insulin treatment, absence of obesity or absence of family history of T2DM).

By definition, it exists before pregnancy but may not have been recognized beforehand, and is thus present as GDM and...
only detected after pregnancy. It poses differential diagnosis problems and will not be discussed here.

2.7. Screening for T2DM after GDM

2.7.1. Contraception and breast feeding

These do not affect the results of screening and should not delay it (see: Kerlan V. Post-partum and contraception in women having had gestational diabetes).

2.8. Are there patients who are more at risk than others?

2.8.1. Main risk factors: being overweight, early diagnosis, insulin treatment, glycaemia.

The systematic review by Baptiste-Roberts et al. in 2009 [76] covered 14 studies and 9 categories of risk factors. Three factors were consistently and highly associated with the incidence of T2DM: anthropometric weight characteristics; insulin treatment; and, among the linked variables, women declared positive during early screening. The authors underline the significant heterogeneity of analysis methods used in the studies and the absence of studies combining risk factors. It should be noted that family history was not always studied.

The influence of glycaemia during pregnancy on the incidence of T2DM was studied in the systematic review of 11 prospective studies by Golden et al. [77]. In five studies, fasting glycaemia for HGPO during pregnancy was a good predictor of T2DM onset and in three studies glycaemia at 2 hours, the thresholds used were variable but the risk increased with glycaemia. Risk associated with the one-hour-glycaemia was evaluated in very few studies.

2.8.2. Combining risk factors

The only study combining risk factors has just been published by Schaefer-Graf et al. [8]. In this German prospective multicentric study, the initial cohort consisted of 1,184 women; 605 of them came for their OGTT at (median) 13 weeks post partum. The (independent) risk factors were: BMI ≥ 30, gestational age at diagnosis < 24 weeks since last menstrual period (LMP), glycaemia at the first hour of antenatal OGTT > 2 g/L (11 mmol/L) and insulin treatment. With a combination of fewer than two risk factors (59.9% of subjects), there was 1.1% T2DM with an OR = 1.3 (CI 0.7-2.1); with two risk factors (28.5% of subjects) there was 9.2% T2DM with an OR = 4 (CI 2.1-7.6); with more than two risk factors (13.4% of subjects) there was 14% T2DM with an OR = 10.5 (CI 4.5-12.5). Women with two or more risk factors represented 86.6% of post partum T2DM and 67% of other glucose tolerance problems. These factors could identify a key population for screening.

2.8.3. The role of related pre-eclampsia

This was studied by Carr et al. [78] in a retrospective cohort of 2,032 patients having suffered pre-eclampsia and in a control group (n = 29,431) followed for 8.2 years. The incidence of pre-eclampsia during pregnancy was linked to the onset of T2DM (n = 342): HR 1.82 (CI 1.26-2.62) after adjusting for age, primiparity and gestational diabetes. It was comparable without adjustment (1.98 [CI 1.38-2.83]) and in non-GDM patients (n = 30,109) (1.86 [CI 1.22-2.84]). Thus, without being formally conclusive, the risk of T2DM after pre-eclampsia seems to be independent of GDM.

2.8.4. Precarity

This is frequently associated with increased prevalence of T2DM and cardiovascular risk factors. It does not appear to have an independent effect (see: Galtier F. Definitions, epidemiology, risk factors p. xxx). These populations should be closely followed in screening programmes.

2.9. Conclusion

Some factors are associated with a higher risk of T2DM after GDM: excess weight, diagnosis of GDM before 24 weeks, need for insulin treatment, elevated fasting glycaemia and at 2 hours during OGTT for diagnosing GDM (PL2); and glycaemia at one hour (PL4). Family history has not been well studied.

2.10. How to diagnose T2DM after GDM

We remind readers here that diabetes is diagnosed by two abnormal glycaemias: either fasting ≥ 1.26 g/L (7 mmol/L) and/or two hours after OGTT (75 g) ≥ 2 g/L (11 mmol/L). A single glycaemia at any stage during the day > 2 g/L and clinical signs of hyperglycaemia can also diagnose the disease. Impaired Glucose Intolerant is defined by glycaemia at the second hour of OGTT between 1.4 and 2 g/L (7.8 and 11 mmol/L). Impaired fasting hyperglycaemia is defined by fasting glycaemia between 1.00 and 1.25 g/L (5.6 and 6.9 mmol/L) [79].

2.10.1. Current recommendations from various bodies

These are presented in Table 6 [79-80]. Two diagnostic methods are suggested, OGTT or fasting glycaemia.

Early screening by OGTT, six to eight weeks post partum is suggested by all the organisations (screening at three to six months for Alfédim [80]), except NICE [89] who only suggest testing fasting glycaemia. Since 2004 ADA [85] suggests screening using fasting glycaemia as an alternative. ACOG [82] has a more flexible position, screening is not
formally advised, although if done it should be by OGTT because this allows diagnosis of IGT. The Vth Workshop [87] also recommends immediate (2-3 days) post partum glycaemia.

With regard to subsequent follow-up, opinions vary between annual glycaemia testing and glycaemia or OGTT every two to three years.

An annual test of glycaemia is required in case of a glycaemic abnormality (ADA) [85], or in some ethnic groups (ADIPS) [81] or for all (Vth Workshop 2007) [87], (NICE 2008 [89]).

ACOG [82] recommends an OGTT to “screen for IGT in order to offer pre-conception advice”, followed by fasting glycaemia if the OGTT is strictly normal. Since 2006 [83] regular follow-up with fasting glycaemia is recommended in all women having had GDM.

Pre-conception OGTT is recommended by ADIPS [81] and the Vth Workshop [87].

The need to inform of future risks, including cardiovascular risks, and the need for therapeutic education were suggested by Alfédiam in 1997 [80], ADIPS [81], thus over 10 years ago by these two bodies; and more recently by ACOG [82] and

Table 6
How to screen for type 2 diabetes after gestational diabetes? Current recommendations.

<table>
<thead>
<tr>
<th>Country</th>
<th>Immediate post-partum screening</th>
<th>Diagnostic method</th>
<th>Diagnostic criteria g/L (mmol/L)</th>
<th>Further screening</th>
<th>Other recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>France Alfédiam</td>
<td>3 to 6 months after birth</td>
<td>75 g OGTT</td>
<td>WHO</td>
<td>OGTT every 12 to 24 months can be offered</td>
<td>Normalisation or maintenance of weight, regular physical activity, limit other cardiovascular risk factors</td>
</tr>
<tr>
<td>Australia ADIPS Hoffman 1998</td>
<td>6 to 8 weeks post partum</td>
<td>75 g OGTT</td>
<td>≥ At 1 g/L (5.5 mmol/L) fasting; ≥ at 1.26 g/L (7.0 mmol/L) at 2 h</td>
<td>-At least every 2 years; more frequently in some ethnic groups - Pre-conception OGTT could be considered</td>
<td>Importance of warning and advising the woman of the high risk of developing T2DM (diet, physical activity). Careful follow-up of patients with glucose intolerance, at least every 6 months, check for diabetes and other cardiovascular complications</td>
</tr>
<tr>
<td>WHO 1999</td>
<td>6 weeks or work post partum</td>
<td>OGTT 75 g</td>
<td>*Normal: fasting &lt; 1.10 g/L (6.1 mmol/L) and 2 h &lt; 1.40 g/L (7.8 mmol/L) *Impaired fasting hyperglycaemia (IFG) ≥ 1.10 g/L (6.1 mmol/L) and &lt; 1.26 g/L (7.0 mmol/L) *Impaired Glucose intolerance (IGT): 2 h ≥ 1.40 g/L (7.8 mmol/L) and &lt; 2 g/L (11.1 mmol/L) *T2DM: fasting ≥ 1.26 g/L (7.0 mmol/L) or 2 h ≥ 2 g/L (11.1 mmol/L) or both IGT and IFG</td>
<td>Not detailed</td>
<td>Women are at a increased risk of subsequently developing T2DM</td>
</tr>
<tr>
<td>ACOG USA 2001</td>
<td>Screening can be done during post partum visit; not formally recommended</td>
<td>OGTT 75 g better than fasting glycaemia (for 1st screening) and identifies IGT, which is an advantage when counseling on future pregnancies</td>
<td>ADA</td>
<td>In 2006 recommendation [83] for periodic screening by fasting glycaemia, systematic screening after a previous GDM if OGTT and fasting glycaemia were normal post partum.</td>
<td>Patients with IGT should be identified for futur pregnancy counseling</td>
</tr>
<tr>
<td>Gynaeco-Obstetrics society Canada 2002</td>
<td>6 to 12 weeks post partum</td>
<td>OGTT 75 g</td>
<td>WHO 1999</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Sensitivity of the post partum T2DM diagnostic test: fasting glycaemia, OGTT, HbA1c

2.10.2. Sensitivity of the post partum T2DM diagnostic test: fasting glycaemia, OGTT, HbA1c

It is accepted that capillary glycaemia is not sufficient to diagnose diabetes (see: Virally M, et al. Screening and diagnosis methods for gestational diabetes between 24 and 28 weeks pregnancy. p. xx); 75 g/2 hour OGTT is the reference method in epidemiology. Its limits in clinical practice (low reproducibility) [91] as well as its cost, discomfort and low level of compliance have been highlighted, including after GDM (see below: paragraph Feasibility of screening and lifestyle changes and Table 7).

It was to counterbalance these practical difficulties that screening by fasting glycaemia was proposed, although its sensitivity was shown to be sub-optimal in the DECODE study in 1998 [92]. Its performance in diagnosing post-GDM T2DM was analysed by a systematic review (13 transversal studies) [93]. The conclusion was that fasting glycaemia alone lacked sensitivity, with variations between 16 and 89%.

Subsequent studies reach same conclusion. Sensitivity for the diagnosis of T2DM in three retrospective studies was only 28% in a Canadian study of a mixed population (n = 909) [94]; 25% in an American study (NDDG criteria; n = 600) [95]; and 74% in a multicentric British study (n = 470) of a mixed population (15% Asian and Carribean) where incidence of obesity was almost 30% [10]. It is 76% in a prospective Australian study of a mixed population (n = 1,077) 6-8 weeks post partum [96]. The only recent study reporting good sensitivity was on a small population (n = 39) [97].

<table>
<thead>
<tr>
<th>Country</th>
<th>Immediate post-partum screening</th>
<th>Diagnostic method</th>
<th>Diagnostic criteria g/L (mmol/L)</th>
<th>Further screening</th>
<th>Other recommendations</th>
</tr>
</thead>
</table>
| ADA 2004 [85] | 6 weeks or more post partum | Impaired fasting glycaemia or OGTT 75 g | **Normal:** fasting < 1 g/L (5.6 mmol/L); 2 h < 1.40 g/L (7.8 mmol/L)  
**Fasting hyperglycaemia:** ≥ 1.00 g/L (5.6 mmol/L) and < 1.26 g/L (7.0 mmol/L);  
**Impaired glucose tolerance:** 2 h ≥ 1.40 g/L (7.7 mmol/L) and < 2 g/L (11.1 mmol/L)  
**T2DM:** fasting ≥ 1.26 g/L (7.0 mmol/L) or 2 h ≥ 2 g/L (11.1 mmol/L)  
or clinical + random glycaemia ≥ 2 g/L (11.1 mmol/L) | **Renewed:** - every 3 years if glycaemia was normal (every 1-2 years [86])  
- every year in case of impaired tolerance or moderate fasting hyperglycaemia. | - All patients should be educated for lifestyle changes (diet, physical activity to maintain normal weight)  
- In case of glucose intolerance or moderate fasting hyperglycaemia, intensive dietary counseling and personalized advice on physical activity |
| Vth internat. Workshop conference on GD USA Metzger 2007 [87] | - Immediately post partum (1-3 days)  
- 12 wks post partum (during post natal checkup) | Birth: fasting glycaemia or random;  
6-12 weeks pp: OGTT 75 g | ADA -OGTT 75 g after one year  
- Then every 3 years  
- Between tests: annual fasting glycaemia | Before next pregnancy |
| France HAS 2006 [88] | Very variable risk, real incidence of T2DM after GDM unknown | - | - | Very variable risk, real incidence of T2DM after GDM unknown |
| UK NICE 2008 [89] | 6 weeks post partum | fasting glycaemia alone ≥ 1.26 g/L (7.0 mmol/L) | WHO - OGTT or fasting glycaemia before next pregnancy | Patient education: balanced diet, normal weight, physical activity. Know signs of diabetes. |

NICE [89]. Some organisations, influenced by the results of the DPP Study [90] (see: paragraph Feasibility of screening and lifestyle changes propose more intensive support for all women (Vth Workshop) [87], or only in cases of glucose tolerance disorders (ADA) [85].
Table 7
Post-Partum Screening Rates For Type 2 Diabetes Mellitus After A Gestational Diabetes

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type, year</th>
<th>n</th>
<th>Screening method and results</th>
<th>Time since giving birth</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conway et al.</td>
<td>Observational study 1999 [118]</td>
<td>179</td>
<td>OGTT: 17.6%</td>
<td>4 to 6 weeks</td>
<td>Laboratory collaboration ensured</td>
</tr>
<tr>
<td>Kaufmann et al.</td>
<td>Retrospective study 1999 [119]</td>
<td>66</td>
<td>Annual OGTT for 5 years: 30.3% Screened at least once: 43%</td>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td>Schaefer-Graf et al.</td>
<td>Retrospective cohort 2002 [120]</td>
<td>1636</td>
<td>OGTT: 46%</td>
<td>4 to 16 weeks</td>
<td>Linked with screening: young age, no previous GDM No other demographic or neonatal parameters associated; glycaemia</td>
</tr>
<tr>
<td>Clark et al.</td>
<td>Case series 2003 [121]</td>
<td>254</td>
<td>OGTT: 0% and 0% Fasting glycaemia: 75% then 92.3% (p &lt; 0.01) HbA1c: 11.6% then 38.5% (p &lt; 0.05)</td>
<td>2 to 52 weeks</td>
<td>Comparison of two historic series: Old/new recommendations</td>
</tr>
<tr>
<td>Smirnakis et al.</td>
<td>Retrospective cohort 2005 [122]</td>
<td>197</td>
<td>OGTT or fasting glycaemia: 37% Any test: 67%</td>
<td>1 to 14 months</td>
<td>98% of these women carry out other tests (cervical cancer) with shorter intervals. Associated with high glycaemia. No associated with education level, age, race, BMI, primary language, median income, insurance level.</td>
</tr>
<tr>
<td>Russel et al.</td>
<td>Retrospective cohort 2006 [123]</td>
<td>344</td>
<td>OGTT or fasting glycaemia: 45%</td>
<td>6 weeks</td>
<td>Linked with screening: attendance to post partum visit (RR = 3.74 [CI 2.14-6.52] p &lt; 0.001; RR = 3.04 [CI 1.72-5.34] after adjustment) Not linked to screening: age, tobacco use, education, marital status, previous GDM, BMI, parity, C-section, infant weight, premature birth</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Retrospective study 2006 [124]</td>
<td>447</td>
<td>OGTT or fasting glycaemia: 23% Any test: 38%</td>
<td>&gt; 6 weeks</td>
<td>Factors in favour: married, followed by an endocrinologist, repeated consultations. Not linked: insulin treatment, number of prenatal consultations or consultation with an obstetrician</td>
</tr>
<tr>
<td>Almario et al.</td>
<td>Transversal study 2008 [125]</td>
<td>90</td>
<td>OGTT or fasting glycaemia: 20% if prescribed by obstetrician, If screening is carried out by another practitioner: 33.3%</td>
<td>5-12 weeks</td>
<td></td>
</tr>
<tr>
<td>Hunt et al.</td>
<td>Prospective cohort 2008 [126]</td>
<td>707</td>
<td>OGTT: 41% Fasting glycaemia: 15.8%</td>
<td>94% within 12 weeks</td>
<td>57% of the initial prospective cohort screened; linked with screening: less severe GDM, not treated with insulin; more obese.</td>
</tr>
<tr>
<td>Dietz et al.</td>
<td>Transversal study 2008 [127]</td>
<td>461</td>
<td>Fasting glycaemia: 9% (in 1999) 57.8% (in 2004)</td>
<td>Within 3 months post partum</td>
<td>No medical prescription for 20% of women in 2004</td>
</tr>
<tr>
<td>Morrison et al.</td>
<td>Transversal study 2009 [128]</td>
<td>1,372</td>
<td>73.2% answered, OGTT: 27.4%</td>
<td>6 to 8 weeks</td>
<td>Linked factors: receiving personalised advice (OR 1.14 [1.08-1.84]) written information (OR 1.35 [1.03-1.76]), being followed by an endocrinologist and not being tertiary educated (OR 2.09 [1.49-2.93]) seeing an obstetrician or diabetes educator during pregnancy(OR 1.72 [1.19-2.48])</td>
</tr>
<tr>
<td>Clark</td>
<td>Randomised study of intervention 2009 [129]</td>
<td>121</td>
<td>Without reminder: OGTT 1.43% Fasting glycaemia: 40%; HbA1c: 17.1% If both doctor and patient reminded: OGTT 60.5% Fasting glycaemia: 63%; HbA1c: 8.6%</td>
<td>1 year</td>
<td>In case of written reminder to the doctor and patient, 75.3% (p &lt; 0.05) carry out any test</td>
</tr>
<tr>
<td>Lawrence</td>
<td>Retrospective study 2010 [130]</td>
<td>5939</td>
<td>OGTT: 10% Fasting glycaemia: 40%</td>
<td>1 to 26 weeks</td>
<td>Post-partum testing associated with age, race, household income, education, parity, mode of delivery, post partum visit, treated for diabetes</td>
</tr>
</tbody>
</table>
The sensitivity for diagnosis of various glucose tolerance problems is only 73% in a retrospective study (n = 985) in a mixed population 10 years after GDM [98]; 38% in the study by Ferrara et al. [95].

HbA1c assays are simple and well accepted. Intra-individual (< 2%) and inter-assay (< 5%) variability are very low compared with fasting glycaemia (10%) or OGTT (20 to 30%). The American Diabetes Association (ADA) has included it as a test to diagnose diabetes [99]. The European Association for the Study of Diabetes (EASD) will also include it shortly. The threshold for diagnosis of diabetes (> 6.5%) seemed to lack sensitivity [100], as it varies between populations [101]. A level between 5.5 and 6.5% indicates a higher risk of diabetes [102]. Although it now seems that HbA1c was not detecting the same diabetic patients [101]; it could better select patients at risk of macroangiopathy. It is of note that it is not possible to assay this marker in all regions of the world, and no study evaluating HbA1c in the diagnosis of post-GDM T2DM has been published.

To date, the use of HbA1c for diagnosis is not recommended by the French diabetes society (SFD), although it is in the United States, Germany and Scotland.

The only cost-effectiveness study, published as part of post-GDM screening for T2DM every 1, 2 or 3 years, showed that OGTT every 3 years offered a lower cost per T2DM case detected, compared to fasting glycaemia or HbA1c. But the latter two became less costly if fewer OGTT were carried out [103].

2.11. Conclusion

After GDM, screening for T2DM by fasting glycaemia is less sensitive than by OGTT (PL1). Screening using HbA1c is simpler than OGTT. HbA1c is much less variable than fasting glycaemia or OGTT. Its use is already recommended by several foreign learned bodies, but not by the SFD as of today.

3. Prevention of type 2 diabetes

3.1. What prevention should be used?

Prevention by breast-feeding is discussed in other publications (see: Kerlan V. Post partum and contraception in women having had gestational diabetes. P xxx)

3.1.1. Observational studies of diet

Zhang et al. report an after-the-fact observational study (cohort from the Nurses’ Health Study [104]) on the role of diet. A high amount of fibre (> 22 g/day) in the diet of women having had GDM is linked to a 33% reduction in risk of T2DM (OR 0.67 [CI 0.51-0.90]). The risk of diabetes is lowered further when the diet is balanced, with an appropriate level of lipids and rich in fibre.

3.1.2. Intervention studies to modify lifestyle after a pregnancy with GDM

Wein et al. [105] carried out a small randomised study (n = 22) of Australian women with GDM who became glucose intolerant and were followed-up for four years. In the control of glucose tolerance, these authors showed an absence of efficacy of intensive dietary support when not combined with advice on physical activity.

Stage et al. [106] carried out a non-randomised retrospective study (n = 121) where patients were given information on their risk of T2DM after GDM and on the importance of lifestyle modifications without a coaching programme. After a two-year follow-up, 16% T2DM and 18% IGT patients were identified. Among the women whose BMI was greater than 25, only 18% had lost more than 5 kg and 33% had put on weight after giving birth, although 86% were aware of the risk of developing T2DM. The level of physical activity had not increased (36 inactive before pregnancy versus 47 after). Fewer women had reduced their fat intake (90 before pregnancy versus 58 after).

The literature is therefore quite sparse with regard to studies of classical intervention after GDM and those that exist appear to indicate inefficacy. However, it should be noted that, post partum, in women without a history of GDM, randomized studies of intervention for weight loss based on diet and physical activity have shown their efficacy (systematic review by Keller et al. in 2008 [107]).

3.1.3. Studies of pharmacological intervention using glitazones alone after GDM

Two studies were carried out in Latino-American patients. Troglitazone was tested against placebo in a randomised study (TRIPOD study, Buchanan et al. [108]) in 266 patients, with average: BMI 30, age 34, four years after GDM (Carpenter and Coustan; 2/3 IGT). The risk of T2DM was reduced by 55% (5.4 % per year versus 12.1% per year). Eight months after the end of the study, the incidence of T2DM remained low: 3.1 % per year versus 21.1% per year. This drug therefore allowed T2DM prevention, or at least delayed its appearance. The aortic intima-media thickness was reduced [109].

This drug has since been withdrawn from the market due to hepatic toxicity; the patients that did not develop T2DM (n = 82) were given pioglitazone, 30 then 45 mg, for three years (PIPOD study) [110]. The annual incidence of T2DM was reduced by two third (4.6% per year, versus 12.1% per year in the placebo arm of the TRIPOD study) as was aortic intima-media thickness [111]. This effect was also seen in at-risk populations without a history of GDM.

3.2. Conclusion

**Tro- and pioglitazone are effective in preventing T2DM after GDM in overweight patients with minor glycoregulation problems (EL2).**

Although the level of proof is adequate, pioglitazone cannot be used because of its recent introduction, the risk of distal fractures, the lack of hindsight for prolonged use, its cost. There is also no authorisation for this indication.

3.2.1. Intensive intervention studies and pharmacological prevention have proven their effect

Women without GDM, these studies are very effective in the prevention of T2DM in at-risk populations, without specific mention of history of GDM (systematic review and meta-analysis by Gillies et al. [112]). For example in the DPP study [113], weight loss (5 kg) was strongly linked to a reduced risk of diabetes (HR: 0.42 [CI 0.35-0.51]). DPP interventions had a good cost/effectiveness ratio [114]. Efficacy persists beyond the end of interventions: 5.7 years after the end of the study, the incidence of T2DM in the «metformin» arm was reduced by 18% and in the «lifestyle modifications» arm by 34%, compared to the placebo arm [115]. Three years after the end of the Finnish prevention study, a similar 36% reduction was noted in the intensive lifestyle modifications group [116].

Finally, a «Cochrane» meta-analysis in 2008 [117] analysed the impact of diet alone (one study), of physical activity alone (one study) or a combination of the two (eight studies). Physical activity and/or dietary modifications reduce the risk of T2DM compared to standard advice (RR 0.63 [CI 0.49-.79]) (EL1 to 2).

Women without GDM as indicated above, the DPP study included patient with already minor glycemic anomalies [11]. Patients were included in the following three arms: standard intervention, with lifestyle advice twice per year and placebo; metformin (850 mg twice daily); intensive intervention with placebo, «coaching» by regular dietetic interviews and performing 30 to 60 minutes physical activity per day at least five days per week. An analysis focused on women who had GDM.

In the placebo arm, the global incidence of post-GDM T2DM (adjusted for age) was 15.2 per 100 person-years versus 8.9 in patients without a history of GDM (p < 0.05), on average 12 years after GDM. Intensive lifestyle modifications or metformin had the same observable efficacy, compared to placebo: they both more than halve the incidence of T2DM (53.4% and 50.4%, respectively. p < 0.05 in both cases).

In terms of reducing the incidence of T2DM, metformin was three times more effective where there was a history of GDM versus not (50.4% versus 14.4% reduction). This effect could be explained by the younger age of patients with a history of GDM as metformin efficacy drops after 60 years of age [11].

Whether using metformin or with lifestyle modifications, the number of patients who needed treatment was very low, between five and six, to avoid T2DM over a 3-year period (24 and 9, respectively, in the absence of a history of GDM).

It should be noted that BMI were high (GDM versus non GDM: 34.2 ± 6.2 versus 34.6 ± 6.8). Thus, in the DPP study, 68% of the GDM patients included had a BMI between 28 and 40 (of which more than half were > 34); 17% had a BMI > 40 and 17% a BMI < 28. There were therefore a maximum of 15% of women of normal corpulence in this cohort.

Intervention therefore has a proven positive effect in this sub-group of women, but can it be extrapolated to women of normal corpulence? The proportion of such women having glucose tolerance anomalies should not be underestimated, as it was evaluated at least 50% across all ethnic groups (except for Latino-Americans who present more obesity) in the review of Kitzmiller et a[12]. In fact, we do not have studies investigating prevention of T2DM after GDM in normal BMI women, which would allow us to answer this question.

3.3. Conclusion

After GDM, in overweight or obese patients with minor glycoregulation problems, lifestyle modifications reduce the risk of T2DM by half (EL2).

Metformin also reduces the risk of T2DM by half after GDM in overweight or obese patients suffering from minor glycoregulation disorders. This reduction is three times greater than that seen without a history of GDM (EL2).

3.4. Feasibility of screening and lifestyle changes (Table 7)

3.4.1. A small proportion of patients are screened for T2DM after GDM

These results are presented in Table 7 [118-130]. Most studies find a low rate of screening, between 15 and 50%, slightly higher in specific cases (written or postal reminder) [128, 129] or up to 92% in the case of highly involved obstetricians [121]. OGGT is carried out less often, around 20% generally (between 0 and 47%) than fasting glycaemia, generally over 50% (between 16 and 92%).

3.4.2. The risk of future diabetes is not fully perceived

The case-control study carried out by Feig et al. [131] between three and five years after pregnancy revealed that 47% of patients thought they were at high risk, while 35% thought they were at low risk.
In the transversal study by Kim et al. [132] (n = 217) with a control group, 90% of women knew that T2DM could appear, but only 16% thought themselves to be directly concerned. The women evaluating their risk as moderate or high were more often obese or had a family history of diabetes and they more frequently planned lifestyle changes (9.1 [0.16-0.92]).

Some women “forget”. In the transversal study of white college educated women (n = 228), Kim et al., [133] explored memory of advices relating to screening for future DT2 and given during pregnancy. No significant association existed between recall of advice and physical activity or between recall of advice and diet. But recall of advice along with distribution of laboratory slips for glucose testing was associated with performance of postpartum T2DM screening using self reports (adjusted OR 2.07 [CI 1.51-2.84]) or claims data (adjusted OR 1.64 [CI 1.16-2.32]).

Hunt et al. [126] showed in a prospective cohort (n = 707) that women who did not present for screening had a more serious GDM, requiring insulin treatment.

3.4.3. Some socio-cultural factors and types of management have a favourable influence on screening (Table 7)

Presentation at the post partum consultation (in a specialized centre) improved compliance with subsequent screening, in four studies [123, 125, 126, 128].

Receipt of a letter considerably increased compliance with all types of screening (OGTT, fasting glycaemia) [128, 129].

The self-administered survey by Morrison et al. [128] in Australia found the following factors to be linked to compliance to postnatal testing: specialist diabetes care in non-tertiary educated women, team approach with diabetes education and obstetric care, individualised follow up from a health professional and provision of written information.

Linked factors:

Other factors, such as availability of these mothers, were not explored.

3.4.4. Difficulties applying lifestyle changes

There are different reasons for these difficulties.

Firstly, patient beliefs, as the two Scandinavian studies showed. In an observational study (n = 113) with a control group, women having had GDM (n = 226) were more worried about their health and more often changed their diets (34% versus 13%, p < 0.001) [134]. In contrast, in a series of cases (n = 121), 86% of women were worried, but only a minority changed their lifestyles [135]. This lack of change in habits despite an appropriate perception of risk was found both after GDM and outside GDM in other populations at risk of T2DM [136, 137].

Low level of motivation for changes to dietary habits and/or physical activity is found in the following five transversal studies.

A low level of physical activity was linked to an absence of social support and a sense of self-efficiency [138]. Women with a history of GDM (n = 4,718) who lived with their children ate significantly fewer fruit and vegetables (OR 0.78 [IC 0.63-0.97]) and smoked more (OR 1.21 [IC 1.01-1.47]); they were not more physically active [139]. In a study drawn from the “behavioural risk factor surveillance”, women with a history of GDM (n = 2,123) were more frequently physically inactive (OR prevalence = 1.4 [1.2-1.7]) [140]. In a programme aiming to modify physical activity and diet (n = 238), social support and self-motivation were linked to increased physical activity, but this was not observed in cases of obesity [141]. A telephone survey 6 to 24 months after GDM (n = 226) found that only 5% of women ate five fruits or vegetables per day and 44% ate two or more [142].

Semi-directed interviews exploring perception of physical activity showed that under-estimation of personal efficiency, lack of time, lack of spousal support and lack of childcare where consultations were made could explain a lack of participation in physical activity [143, 144].

Finally, depression can also play a role. In a retrospective cohort with control (n = 886) an increased risk of depression is observed in some low-revenue populations after insulin-treated GDM (n = 163) (adjusted OR 2.03 [CI 1.33-3.11]) or untreated GDM (n = 183) (adjusted OR 1.72 [CI 1.11-2.66]).

3.4.5. Difficulties mobilising and informing medical teams of the medium- or even short-term risk of developing T2DM (Table 7)

Gabbe et al. [146] showed that only 60% of obstetricians offered screening, 39% using 75g OGTT. Only 62% thought that these women were at risk of developing T2DM. Six years later, in 2004, the same author found slightly higher figures (screening: 57% and use of OGTT: 50.8%). Clark et al. [121] showed that the new Canadian recommendations, issued in 1998, did not increase the number of women screened for T2DM using OGTT, because none had taken advantage of this screen. On the other hand, screening by fasting glycaemia or HbA1c assay had increased. Almario et al. [125] showed that only one third of 90 women had had the ADA recommendations passed on by their doctors.

4. Conclusions

Analysis of the literature leads to the suggestions below.

The high risk of T2DM after GDM justifies screening for this disease.
How to proceed? Capillary glycaemia is not precise enough to diagnose T2DM. At the postnatal consultation, OGTT can identify T2DM or glucose intolerance. HbA1c assay, recommended by the ADA and soon to be by the EASD, is simpler, better accepted and less variable than fasting glycaemia and OGTT. Breast feeding or contraception do not affect diagnosis. Evaluation of subsequent glycaemic status should be maintained long-term as the risk has been shown to persist for at least 25 years; it is indispensable in cases where a new pregnancy is desired. This requires participation from all parties: general practitioners, gynaecologists, obstetricians, mid-wives, endocrinologists, maternal and child-care teams, family planning centres etc... without forgetting the patients themselves, who must be informed of the risks resulting from GDM during their pregnancy.

Some factors are associated with an higher risk: weight excess, appearance of GDM before 24 weeks pregnancy, high prenatal fasting glycaemia or at 2 hours during OGTT and insulin treatment. Screening women combining two or more of these risks could optimize efficacy.

Systematic screening for T1DM after GDM by anti-GAD antibodies is not necessary unless there is some additional clinical reason: family or personal history of auto-immune disease, insulin treatment during GDM or no obesity or no family history of T2DM.

How to prevent T2DM? In all women, follow-up must encourage lifestyle changes (30 to 60 minutes physical activity per day at least five days a week, balanced diet, quitting smoking). Follow-up should also include regular screening and treatment of any other associated cardiovascular risk factors (hypertension, dyslipidaemia). Finally, glycaemic status should be evaluated every three years; the interval should be shortened in case of weight gain.

For women with risk factors for T2DM (overweight or obesity, diagnosis of GDM before 24 weeks gestation, need for insulin treatment or high glycaemia during OGTT diagnosing GDM), the evaluation mentioned above should be annual and therapeutic education should focus on lifestyle changes.

In overweight patients who already have minor glycoregulation anomalies (fasting glycaemia between 1.00 and 1.25 g/L or 5.6 and 6.9 mmol/L; glycaemia at 2 hours of OGTT between 1.4 and 2 g/L or 7.8 and 11 mmol/L) (maybe later diagnosed by HbA1c between 5.7 and 6.5%), lifestyle changes are very effective in preventing T2DM. In addition to the follow-up described above, these patients should integrate targeted therapeutic education programs. Metformin halves the risk of T2DM. The fact that it has been used for a long time, is generally well tolerated, the apparent very low teratogenic risk and its low cost make it the drug of choice. However, contrary to the United States, it does not have the necessary authorization to be used for this indication in France.

For women who are already diabetic (fasting glycaemia > 1.25 g/L or > 7 mmol/L and glycaemia at 2 hours of OGTT > 2 g/L or > 11 mmol/L) (maybe later diagnosed by HbA1c > 6.5%) it is particularly important that they benefit from therapeutic education covering the management of T2DM to stabilize the disease: lifestyle, weight control, management of the quality of glycaemic balance, aims of treatment and how it should be applied, prevention of microangiopathy complications and other vascular problems. These are all considerable challenges at this early stage of the disease.

Last but not least, in case of glycaemic status anomalies, it is very important that therapeutic education also includes planning of future pregnancies to reduce the risks of malformations and miscarriages.

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6. Conflict of interests

No conflict of interests related to the article.

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