Relevance of gestational diabetes mellitus screening and comparison of selective with universal strategies

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Abstract

Objectives: To assess the relevance of gestational diabetes mellitus (GDM) screening policies and to compare selective with universal screening.


Results: Maternal hyperglycaemia is associated with increased maternal and neonatal complications. The 75g OGTT (Oral Glucose Tolerance Test) is a valid and reliable test for GDM diagnosis. Treatment of GDM reduces perinatal complications.

Selective screening helps limit false positive rates and concentrate medical resources. Nevertheless, screening could be more difficult and lead to missing up to 45% of GDM cases.

Universal screening offers higher sensitivity but leads to more therapeutic interventions whose benefit and cost/effectiveness ratio need to be estimated in low risk women.

Conclusion: The benefits of GDM screening and treatment have only been proven for women with GDM risk factors. Their relevance in women without risk factor remains controversial.

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

Résumé

Objectifs : Évaluer l’intérêt du dépistage du diabète gestationnel et comparaison des stratégies ciblée et systématique


Résultats : L’hyperglycémie maternelle est associée à une augmentation des complications maternelles et néonatales. L’HGPO (Hyperglycémie provoquée par voie orale) à 75 g est un examen valide et fiable pour le diagnostic de DG. Le traitement du DG permet de diminuer l’incidence de ses complications. Le dépistage ciblé permet de limiter le nombre de faux positifs et de concentrer les moyens. Cependant, il peut s’avérer complexe et conduire à méconnaître jusqu’à 45 % des cas de DG. Le dépistage universel est plus sensible, mais engendre plus d’interventions thérapeutiques dont le bénéfice et le rapport coût-efficacité restent cependant à évaluer dans les populations à faible risque.

Conclusions: Les bénéfices d’un dépistage du DG et de la prise en charge qui en résulte n’ont été mis en évidence que chez les patientes présentant des facteurs de risque de DG. Leur intérêt chez les patientes ne présentant aucun facteur de risque reste controversé.

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

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1. Introduction

The evaluation of a screening policy in a population must answer the following questions: should we screen? If yes, who? When? And how?

In the case of gestational diabetes mellitus (GDM), the amount of publications, the heterogeneity of definitions used and the diversity of screening methods makes for a complex collection of data, giving rise to diverse and sometimes contradictory answers from the scientific community.

Our objectives were to answer two of these questions: are there convincing data that help justify creating a GDM screening policy? And if yes, should it be for the entire population of pregnant woman or just reserved for higher risk patients?

2. Materials and methods

We carried out systematic searches on Medline and the Cochrane Database for articles in English and French on the epidemiology, complications, screening, treatment and medical-economic data on GDM published between 1990 and 2010. A second search was carried out for selective and universal screenings.

Each search was completed with a manual search of referenced articles in the selected articles.

For the first part of our research on the relevance of screening, the MeSH expression “gestational diabetes” was repeatedly associated with the terms: “prevalence”, “epidemiology”, “mortality”, “morbidity”, “screening”, “diagnosis”, “reproducibility”, “treatment” and “cost-benefit analysis”.

For the second part on selective and universal screening, the expression “gestational diabetes AND screening” was associated with the terms: “selective” and “universal.”

2.1. Relevance of screening gestational diabetes mellitus

2.1.1. Definitions

Diagnosis is an individual undertaking for a symptomatic patient in whom you seek to confirm the existence of a curable or incurable disease.

Screening is part of public health policy. Its aim is to isolate within a targeted population individuals presenting risk factors or at an asymptomatic stage in a given disease in order to prevent it (primary prevention), treat it, thus lowering its prevalence (secondary prevention) or limit chronic complications or relapses (tertiary prevention). When screening for a particular disease, it can be universal (or “massive”) for all individuals within a targeted population; or targeted (or selective) and only be for individuals with risk factors for the disease.

2.1.2. General concept of screening

Screening is considered to be pertinent when, along with the resulting intervention, it aims to decrease the morbidity and/or mortality in a population [1]. The criteria that can help increase the validity of a screening policy are disease prevalence in a population, the quality of screening tests and, potentially, diagnostic exams, the efficacy of resulting interventions and, finally, the economic consequences (cost-effectiveness ratio).

2.1.3. Epidemiology

The prevalence of GDM is estimated to be between 1 and 22% of pregnancies (see question 1 – F. Galtier). This variability in estimates is a reflection of the disparity in populations studied (prevalence of risk factors) and screening methods (tests and thresholds used). In France, the estimation provided by Audipog is around 4% [2]. Estimations of the proportion of diabetes during pregnancy vary between 10% and 40% of cases of diabetes present during pregnancy (see question 5 – A.M. Guedj). In some of these cases, diabetes was unrecognized (type 2 diabetes) and wrongly confused with GDM.

2.1.4. Consequences

2.1.4.1. Perinatal

The association of GDM and high perinatal mortality risk remains controversial (see question 3 – D. Mitanchez). The oldest data show a relative significant risk estimated between 2 and 4 [3-5] (EL4). However, the populations studied lacked heterogeneity, mixing preexisting diabetes and true GDM. This association was not confirmed by the HAPO (Hyperglycaemia and Adverse Pregnancy Outcomes) study results on 23,000 pregnant women with no preexisting diabetes and whose results of the 75g oral glucose tolerance test (OGTT) given between the 24th and 32nd weeks of pregnancy remained blind for the entire pregnancy [6]. However, patients with fasting glycaemia over 1.05 g/L, 2 g/L at 2 h or 1.6 g/L with a random dosage were excluded from this study and were given appropriate care. Their results are therefore unavailable and the absence of a link between maternal hyperglycaemia and therefore perinatal mortality cannot be affirmed. The risk could exist in patients with high hyperglycaemia equivalent to cases of preexisting diabetes before pregnancy [7].

However, the association between GDM and neonatal morbidity has been clearly established [6, 8] (EL2). The results of the HAPO study demonstrated a positive correlation between maternal glycaemia during pregnancy and incidence of neonatal morbidity [6]. In this study, maternal glycaemia was positively correlated to a risk of macrosomia (birth weight > 90th percentile for gestational age), neonatal hypoglycaemia, premature birth (< 37 WG), shoulder dystocia, obstetrical trauma, NICU stays and neonatal jaundice. However, macrosomia cannot be
considered as intrinsically morbid. It represents an intermediary factor between hyperglycaemia and neonatal morbidities (obstetrical trauma) and maternal morbidities (Caesareans and maternal trauma related to birth) [9].

### 2.1.4.2. Maternal

The existence of GDM is associated with higher maternal morbidity in the short term, mainly via the intermediary factor of foetal macrosomia (EL2) (see G. Beucher). An increase in Caesarean risk before and during labour and in severe perineal tearing (grades 3 and 4) [6, 8, 10] has been observed. Furthermore, incidence of preeclampsia is positively correlated with maternal glycaemia [6, 8, 11]. The correlation is rather moderate, particularly after adjusting for body mass index (BMI). As for neonatal morbidity, there is a dose-effect relationship between glycaemia and the incidence of complications, but without being able to specifically define a threshold under which risks are marginal.

In the long term, a history of GDM is associated with the onset of type 2 diabetes in the years or decades after the index pregnancy [12-16] (EL1). GDM appears to be the first manifestation of disease, preceded by physiological insulin resistance related to the pregnancy that translates to type 2 diabetes after what can be several years. The diagnosis of GDM could also be an opportunity to begin primary preventative measures that are effective in post partum type 2 diabetes [17].

### 2.1.4.3. Socioeconomics

A medical economic analysis from the United States in 2007 has reported that the health costs related to GDM and its consequences were estimated to be $635 million (€490 million) with $595 million going toward care for mothers (prenatal and post partum periods) and $40 million for paediatric care during the first year of life [18]. This estimate took into account the costs for hospitalizations, regular and urgent care pregnancy check-ups and prescriptions for mothers and their children. With a prevalence of 180,000 cases (4.5% of pregnancies) in the United States in 2007, the cost was estimated at $3,305 per case of GDM. No similar study in the French population could be found.

No data on the social impact and indirect consequences on the global economy (decrease in work time and altered productivity) could be found. It seems probable that the economic consequences of GDM, as with any other disease, go beyond health economics and that its total cost is largely higher than estimates limited to medical care.

### 2.1.5. Screening exams

#### 2.1.5.1. Validity

In the case of GDM, the evaluation of the validity of screening tests is difficult. The tests used have a dual function of screening and diagnosis; none of the tests available can be considered as a reference test. The performances of the different tests can only be estimated by their ability to predict the onset of perinatal and maternal complications. The only data available are found in the HAPO study that confirms the association between maternal glycaemia and obstetrical and neonatal complications [6]. The secondary analysis of these data helped the IADPSG (International Association of Diabetes and Pregnancy Study Group) to propose the following pathological glycaemia thresholds [19]: fasting glycaemia ≥ 0.92 g/L, post prandial glycaemia at 1 h ≥ 1.80 g/L, post prandial glycaemia at 2 h ≥ 1.53 g/L after a 75g OGTT between 24 and 28 WG (see question 7 – E. Cosson). The thresholds were chosen based on an odds ratio equal to 1.75 for the onset of an unfavourable outcome of the pregnancy in patients with at least abnormal glycaemia levels (the control group was made up of patients with lower than average glycaemia levels). Using these thresholds, 17.8% of patients eligible for the HAPO study had at least one pathological glycaemia level and could be considered to have GDM. Among them, 1.7% of patients were excluded from the study for having over-high glycaemia levels that required informing them and providing appropriate medical care.

The combined use of several glycaemia measurements helped increase prediction sensitivity, but at the cost of increasing the rate of false positives. In the HAPO study, the sensitivity of each of the three glycaemia levels used independently did not exceed 20% for predicting macromsomia and 15% for predicting Caesareans before labour and symptomatic neonatal hypoglycaemia. The rate of false positives was estimated to be around 10%. The combination of the results of the three dosages helped increase sensitivities to 27%, 22% and 21%, respectively, for predicting each of the complications (sensitivity calculated by us from the HAPO study results and its secondary analysis) [6, 19].

#### 2.1.5.2. Reliability

The rate of reproducibility (proportion of similarity of glycaemia levels beyond a threshold between two tests carried out at an interval of at least 24 hours) was estimated to be 83% for 50g OGTT and between 76 and 78% for 100g OGTT [20-22] (see question 6 – M. Virally). For 75g OGTT, a quantitative evaluation of 60 patients at 27 WG did not show any significant difference between each glycaemia level (H0, H1 and H2) for two OGTT carried out at three-day intervals [23]. The 75g OGTT therefore seems to have good reproducibility (EL2).

#### 2.1.5.3. Acceptability and side effects

The acceptability of a screening policy by a population depends mainly on the simplicity of the screening methods, constraints related to care in case of a positive result and potential adverse events. A positive result for a screening test could be a source of adverse psychological consequences in patients and higher medical costs. The perception of having
a difference appears to have higher anxiety just after the screening compared to patients with a negative test result. However, this difference seems to be minimal and is not demonstrated in the mid-term (before giving birth) and long-term (post partum) [25, 26] (EL2). In some studies, a positive screening result is experienced by some patients as an alteration in their or their child’s state of health; this perception remains through the mid- and long-term [26-29] (EL2). Medical care (diet or insulin therapy) does not seem to change this perception [30]. A contrario, in the therapeutic randomized trial by Crowther et al. (Australian Carbohydrate Intolerance Study in Pregnant Women trial Group – ACHOIS), patients informed of the GDM diagnosis and given care judged their physical state to be better compared to uninformed or uncared for patients [31] (EL1). The heterogeneity of results could be the result of using different tools to evaluate mental and physical well-being. No study has shown any difference in the incidence of depressive syndromes [25, 26, 28-30, 32].

A positive screening result is associated with an increased risk in Caesarean delivery, independent of fetal macrosomia (NP2). Naylor et al., in a prospective cohort study of 3,800 screened pregnant patients, showed a significant increase in Caesarean risk estimated to be between 60 and 120% in patients with a positive test result with no fetal macrosomia, compared to patients with a negative test result [33]. In the randomized ACHOIS study, a positive result was associated with an increase in the number of induced births [31] (EL1).

2.1.6. Intervention efficacy

In patients with GDM, medical care (diet, glycaemic monitoring and insulin therapy, if needed) is associated with a decrease in risks of perinatal and maternal complications (EL1) [31, 34-41]. However, the efficacy of medical care on the decrease in Caesarean rates remains controversial.

The meta-analysis by Horvath et al. included data from five randomized studies that evaluated the efficacy of specific medical care in patients with GDM compared to unspecific medical care (2,999 patients) [31, 34, 36-39]. In this analysis, specific care was associated, in children, with a decrease in birth weight and a reduction in risks of birth weights higher than the 90th percentile (OR: 0.48 CI 95% [0.38-0.62]), birth weight over 4,000 g (OR: 0.38 CI at 95% [0.30-0.49]) and shoulder dystocia (OR: 0.40 CI 95% [0.21-0.75]). In women, it was associated with a decrease in the risk of preeclampsia (OR: 0.46 CI 95% [0.22-0.97]). However, in this meta-analysis, initiating care was not associated with a decrease in the frequency of elective or emergency Caesareans (OR: 0.86 CI 95% [0.72-1.02]). Only the randomized trial by Landon et al., included in this meta-analysis with 958 patients, showed a decrease in Caesarean rates in cases of specific care [39]. Caesarean levels were 33.8% in patients not informed of their GDM and not receiving any specific care and 26.9% in patients aware of their GDM and specifically treated for it (diet and sometimes insulin therapy).

Moss et al., in the secondary analysis of data of the randomized ACHOIS trial, calculated that the care for 100 women with GDM could help avoid 2.2 severe neonatal complications and 1 perinatal death [31, 42].

2.1.7. Cost-effectiveness ratio of screening and medical care

The medical/economic evaluation of a screening policy must take into account the cost of the screening test itself as well as costs related to potential adverse events. These costs should be compared to those resulting from treating the expected complications in the absence of screening. It should estimate the consequences of screening in terms of improvement or deterioration of the quality of life of screened subjects and, in the case of obstetrical diseases, their children.

Studies on the subject are rare, contradictory and not really transposable to the French population. They are on Anglo-Saxon populations with a high prevalence of risk factors.

In an economic analysis of a systematic screening policy for GDM in the United States, Nicholson et al. estimated the overall cost of screening GDM to be lower than that resulting from no screening. The cost of screening (OGTT in one or two doses) and its consequences were estimated to be between US$2,836 (€2,100) and US$2,895 (€2,144) per screened subject [43]. The cost of no screening was estimated to be US$2,995 (€2,219) per screenable subject. These estimates included direct health costs related to maternal and paediatric care as well as indirect costs related to loss in productivity or salary for patients.

A contrario, the secondary analysis of data from the ACHOIS trial estimated the cost related to medical care of subjects with GDM to be $6, 050 AUS (€3,993) per treated subject (compared to an absence of care for these subjects). These estimates also included costs related to maternal and paediatric care. From a paediatric point of view, the cost of a year of life saved was estimated to be $2,988 AUS (€1,972) [42].

Overall, the increase in risks of neonatal and maternal morbidity in cases of maternal hyperglycaemia (NP2), the existence of valid and reliable screening tests (NP1) and the acceptable nature of adverse events related to medical care (NP2) favour carrying out GDM screenings.
However, given the heterogeneity of the populations and the screening methods between the HAPO study and other clinical studies, the benefits of medical care for patients diagnosed with GDM based on the guidelines proposed by the IADPSG remain unknown. The anticipated prevalence of GDM diagnosed based on these proposed guidelines is considerably higher than what is observed in clinical trial populations as the number of subjects to treat to avoid adverse events could be much higher than what was observed in the trials. Furthermore, most available data on populations different from the French population in terms of prevalence of risk factors (obesity prevalence and ethnic distribution) limits their external validity. A prospective evaluation of the therapeutic efficacy and cost benefit ratio in a screened population following these methods and comparable to ours is necessary.

2.2. Comparison of selective with universal screening methods

In selective screening of GDM, patients to be screened are chosen based on their case history. Its goal is to limit screening tests in high risk and high prevalence populations to curb screening costs, decrease the number of false positives and thus increase the positive predictive value of these tests.

Universal screening is when all pregnant women are tested. It necessarily implies an increase in the incidence of GDM, at varying rates, depending on the population considered [44].

2.2.1. Risk factors

In selective screening, selection of patients is based on searching for risk factors (see F. Galtier). The factors to consider are medical history, the woman’s state of health at the beginning of the pregnancy and complications arising during the pregnancy. They are as follows:

- family history: type 2 diabetes in one or several first degree relatives;
- medical history: metabolic syndrome, polycystic ovarian syndrome;
- obstetrical history: GDM or macrosomia in a previous pregnancy, unexplained in utero fetal demise;
- maternal characteristics: age (different thresholds), BMI (different thresholds), ethnic origin;
- complications in the current pregnancy: hydramnios, suspicion of macrosomia.

In the literature, the most often used risk factors in selective screening are a history of GDM and macrosomia, age, BMI, ethnic origin and a first degree history of diabetes.

Among these factors, BMI is consistently used in the recommendations for selective screening. There is a strong correlation between being overweight in adulthood and a risk for GDM. In the Nurses’ Health Study (NP2) a BMI > 25 in adults multiplies by 2.36 (CI 95% [2.12-3.77]) the risk of developing GDM [45].

In their meta-analysis, Torloni et al. (NP1) [46] estimated that for each increase of 1 kg/m² of BMI, the prevalence of GDM increased 0.92% (CI 95% [0.7-1.1]). The relative risk of GDM with obesity (BMI > 25 kg/m²), moderate obesity (BMI > 30 kg/m²) and morbid obesity (BMI > 40 kg/m²) was respectively 1.97 (CI 95% [1.77-2.19]), 3.01 (CI 95% [2.34-387]) and 5.55 (CI 95% [4.27-7.21]).

BMI is also associated with a higher risk of GDM in pregnant adolescents. In the study by Khine et al. [47], the threshold of 27 kg/m² helped diagnose 82% of cases of GDM (sensitivity), with a negative predictive value of 99.4% (EL 3).

Aside from BMI, the factors that have the most impact on the risk of GDM are: maternal age (risk multiplied by 3 in the 25-29 age range and by 4 in the 30-34 age range) and a history of gestational diabetes and type 2 diabetes in the immediate family. Ethnic origin only had a moderate impact on the risk of gestational diabetes (see question 1 – F. Galtier).

2.2.2. Risk score

In order to account for the accumulation of several risk factors in one person, some authors have proposed using the risk scores detailed in Table 1.

In the Tri-Hospital Gestational Diabetes Project (EL2) [48] cohort study, a score was established according to the methods detailed in Table 2. The prevalence of GDM increases with the value of the risk score, going from 0.9% for a score ≤ 1 to 18.7% for a score ≥ 6. This score was established based on independent risk factors for the onset of GDM identified in the study, with the number of points attributed to each risk factor being equal to its adjusted odds ratio.

A selective screening strategy based on this clinical score was thus developed:

- score ≤ 1 – No screening;
- score > 1 – Screening carried out with an oral dose of 50 grams of glucose: if the score was between 2 and 3, a threshold of 1.40 g/L (7.8 mmol/L) was used, if the score was ≥ 4, 1.30 g/L was used as the threshold.

The authors reported that this selective strategy helped to obtain a sensitivity and specificity identical to those seen in universal screening and avoid screening with 50 g glucose in 34.6% of women [49]. However, it should be noted that this equivalency in performance is the result of an adjustment of diagnostic criteria since the thresholds selected to confirm GDM were lowered for women who had a higher risk level. In this study, the proportion of GDM that would have been missed with specific screening was 7%.

In a retrospective study on 1,876 Asian women (NP4), the risk of developing GDM was associated with age, BMI, family history of diabetes and history of macrosomia and abortions (Table 3) [50].

A risk score was established as a regression equation integrating the factors independently associated with GDM:
Table 1
Risk score in the medical literature

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Type of study</th>
<th>Definition criteria of risk score</th>
<th>Score performances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naylor [48] 1997, Canada</td>
<td>Retrospective cohort N = 3131 100 g OGTT NDDG criteria</td>
<td>Risk factors Score Age ≤ 30 31-34 ≥ 35 BMI ≤ 22 22.1-25 ≥ 25.1 Ethnic origin Caucasian Afro-American Asian Other</td>
<td>Score according to score rating Score 0 ≤ 1 2 3 4-5 6 GDM Index (%) ≤ 0.9 3.7 3.9 7.3 18.7</td>
</tr>
<tr>
<td>Phaloprakarn [50] 2009, Thailand</td>
<td>Retrospective cohort N = 1876 100 g OGTT Carpenter &amp; Coustan criteria</td>
<td>Risk factors Age &lt; 25 25-34 ≥ 35 BMI &lt; 20 20-24.9 25-29.9 ≥ 30 Family history of diabetes yes no* History of macrosomia yes no* History ≥ 2 abortions yes no*</td>
<td>Score ≥ 380 Sensitivity Specificity 86.9% 45%</td>
</tr>
<tr>
<td>Van Leeuwen [51] 2009, Holland</td>
<td>Prospective cohort N = 995 75 g OGTT WHO criteria</td>
<td>Risk factors Non Caucasian ethnic origin Family history of diabetes Body Mass Index ≥ 22-30 History of GDM Predictive model established using a regression equation integrating risk factors</td>
<td>Sensitivity Specificity 75% 57.8%</td>
</tr>
</tbody>
</table>

Diagnostic criteria of gestational diabetes:
NDDG (National Diabetes Data Group): at least 2 threshold values selected: fasting glycaemia ≥ 5.8 mmol/L (1.05 g/L), glycaemia at 1 hour ≥ 10 mmol/L (1.80 g/L), glycaemia at 2 hours ≥ 9.1 mmol/L (1.65 g/L), glycaemia at 3 hours ≥ 8 mmol/L (1.45 g/L) after oral dose of 100 g glucose.
Carpenter & Coustan: at least 2 threshold values selected: fasting glycaemia ≥ 5.3 mmol/L (0.95 g/L), glycaemia at 1 hour ≥ 10 mmol/L (1.80 g/L), glycaemia at 2 hours ≥ 8.6 mmol/L (1.55 g/L), glycaemia at 3 hours ≥ 7.8 mmol/L (1.40 g/L) after oral dose of 100 g glucose.
WHO (World Health Organization): fasting glycaemia ≥ 7 mmol/L (1.26 g/L) and/or glycaemia -2 h ≥ 7.8 mmol/L (1.40 g/L) after oral dose of 75 g glucose.

Table 2
Risk score created for the Toronto Tri-Hospital Gestational Diabetes cohort [48]

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Score</th>
<th>Odd ratio (CI 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>31-34</td>
<td>1</td>
<td>1.0 (0.7-1.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>≥ 35</td>
<td>2</td>
<td>1.6 (1.1-2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 22</td>
<td>0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>22.1-25</td>
<td>2</td>
<td>1.8 (1.1-2.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>≥ 25.1</td>
<td>3</td>
<td>3.2 (2.1-4.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Afro-American</td>
<td>0</td>
<td>0.7 (0.3-1.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>4.8 (3.0-7.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.6 (0.7-3.5)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Table 3
GDM Risk factors in the study by Phaloprakarn et al. [50]

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR adjusted (CI 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>1.94 (1.51-2.51)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 35</td>
<td>4.27 (2.95-6.20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI 1st visit (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>20.0-24.9</td>
<td>1.68 (1.27-2.22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>25-29.9</td>
<td>3.52 (2.52-4.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 30</td>
<td>8.33 (5.14-13.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>0.73 (0.51-1.04)</td>
<td>0.08</td>
</tr>
<tr>
<td>History diabetes</td>
<td>4.29 (3.07-6.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History macrosomia</td>
<td>6.18 (2.40-15.90)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History ≥ 2 abortions</td>
<td>3.50 (1.36-9.02)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Risk score = 6 × age + 11 × BMI + 109 × family history of diabetes + 42 × history macrosomia + 49 × history ≥ 2 abortions.

Each of the last three parameters was scored 1 if present and 0 if absent.

A ROC curve was created. A score ≥ 380 gave, respectively, sensitivity, specificity, PPV and NPV values of 86.9%, 45%, 41.8% and 88.3%.

Using the data from a prospective study of 995 women (NP2), Van Leeuwen et al. [51] developed a predictive model for GDM that integrated the following characteristics: ethnicity, family history, history of GDM and BMI. This model helped identify 75% of women with GDM and avoid screening in 47% of women at low risk.

### 2.2.3. Performances compared to two screening strategies

#### 2.2.3.1. Performances

In order to compare universal and selective screening, it is necessary to be able to estimate the number of cases of GDM that selective screening would miss and the number of unnecessary tests avoided with this strategy. To that end, general population studies are needed to analyze the prevalence of GDM in relation to the presence of risk factors. Table 4 presents a comparison of these studies and their results.

The proportion of women with GDM that are not diagnosed by selective screening varies between 3 and 10% in most publications [48, 52-56], and can even reach higher than 30%, particularly in the last three French studies [57-59], or even 50% in some series [58, 60]. This is partially related to the impossibility of using obstetrical history in childless women and unfamiliarity with family history.

What is the prognosis of missed cases of GDM in selective screening, i.e. in low risk patients? No study capable of answering this question directly has been found. In the case-control study by Langer et al. [41], unrecognized GDM in women of normal weight (BMI < 25 kg/m²) was not associated with an increase in the incidence of macrosomia or shoulder dystocia (EL4). In the retrospective study by Cosson et al. on 1,515 women (16.6% prevalence of GDM with systematic screening with 75g OGTT), the fœtal/maternal prognosis for women with GDM with no risk factor was similar to that of women without GDM [61]. This is in contrast to the study by Langer et al. [41], in which diabetes in women without risk factors was known and treated. In studies in which selective screening missed few cases of GDM, it is important to consider the proportion of women exempt from screening in the target population. Several studies have reported that screening based on risk factors only averted very few screening tests, which unnecessarily complicated screening [52, 62-64].

On the contrary, other studies report that selective screening has a sensitivity and specificity comparable to those in universal screening but all while avoiding a high number of unnecessary tests [48, 53, 54].

In the retrospective Australian study by Davey et al. [53], comparing selective screening to universal screening, selective screening missed 0.6% of cases of GDM and helped avoid unnecessary screening in 17% of women (EL4).

In the Danish prospective multicentre study by Jensen et al. [54], selective screening missed 7% of cases of GDM and helped avoid biological tests in two thirds of women (EL2).

### Table 4

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Diagnostic criteria</th>
<th>Prevalence of GDM in the population at risk</th>
<th>Selection criteria for the proportion of population at risk</th>
<th>Proportion of GDM in the population at risk</th>
<th>Proportion of GDM missed by selective screening</th>
<th>Authors' conclusions on selective screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietrich [66] 1987, USA</td>
<td>Prospective cohort</td>
<td>N = 2000 100 g OGTT</td>
<td>“Standard” risk factors (not specified)</td>
<td>2.1%</td>
<td>Age &gt; 30, BMI &gt; 22, ethnicity, at risk</td>
<td>4.2%</td>
<td>4.8%</td>
<td>In a patient pool from a private practice, selective screening helped avoid unnecessary tests in more than half of women</td>
</tr>
<tr>
<td>Naylor [48] 1997, Canada</td>
<td>Retrospective cohort</td>
<td>N = 3131 100 g OGTT NDDG criteria</td>
<td>Age &gt; 30, BMI &gt; 22, ethnicity, at risk</td>
<td>3.5%</td>
<td>Score ≤ 1.09% Score ≥ 6 18.7%</td>
<td>7%</td>
<td>A selective screening strategy selecting for clinical risk score is effective and helps many women avoid unnecessary screening</td>
<td></td>
</tr>
<tr>
<td>Moses [56] 1998, Australia</td>
<td>Retrospective cohort</td>
<td>N = 2907 75 g OGTT Glycaemia 2 h ≥ 8 mmol/L (1.45 g/L)</td>
<td>Selection low-risk population: Age &lt; 25, BMI &lt; 25, Caucasian origin</td>
<td>6.3%</td>
<td>low risk: 2.8%</td>
<td>10%</td>
<td>Selective screening is not “reasonable” since low risk does not mean no risk</td>
<td></td>
</tr>
<tr>
<td>Author year, country</td>
<td>Type of study</td>
<td>No. of patients</td>
<td>Diagnostic criteria</td>
<td>Prevalence of GDM in the total population</td>
<td>Selection criteria for the population at risk</td>
<td>Prevalence of GDM in the population at risk</td>
<td>Proportion of GDM missed by selective screening</td>
<td>Authors’ conclusions on selective screening</td>
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<tr>
<td>Williams [64] 1999, USA</td>
<td>Retrospective cohort N = 25,118 100 g OGTT NDDG criteria</td>
<td>ND</td>
<td>Low risk defined as: Age &lt; 25, BMI &lt; 27 Caucasian origin, absence family history of diabetes</td>
<td>ND</td>
<td>4%</td>
<td>No benefit as only 10% of women are exempt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danilenko [52] 1999, USA</td>
<td>Retrospective cohort N = 18,504 100 g OGTT NDDG criteria</td>
<td>3%</td>
<td>Age ≥ 25 BMI ≥ 27, ethnicity, at risk, family history diabetes 10%</td>
<td>low risk</td>
<td>0.9 %</td>
<td>3%</td>
<td>Few missed GDM but too few tests saved for the extra degree of complexity with selective screening</td>
<td></td>
</tr>
<tr>
<td>Davey [53] 2001, Australia</td>
<td>Retrospective case-control N = 6032 75 g OGTT Fasting glycaemia ≥ 5.5 mmol/L (1 g/L) or glycaemia 2 h ≥ 8 mmol/L (1.45 g/L)</td>
<td>5%</td>
<td>Age ≥ 25 or ≥ 30, BMI ≥ 27, ethnicity, at risk, 1st degree history diabetes 17% if age ≥ 25 52% if age ≥ 30</td>
<td>low risk 0.2% if age &lt; 25 1.2% if age &lt; 30</td>
<td>0.6% if age ≥ 25 4% if age ≥ 30</td>
<td>Selective screening is effective and helps reduce the number of tests in certain populations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiménez-Moleon [55] 2002, Spain</td>
<td>Retrospective cohort N = 2574 100 g OGTT NDDG criteria</td>
<td>3.31%</td>
<td>Age ≥ 25 (ADA criteria) or ≥ 30 (ACOG criteria) BMI ≥ 27 or ≥ 30 Family history diabetes History macrosomia History GDM History hypertension History foetal death History congenital defects 45% (ACOG criteria) 15.5% (ADA criteria)</td>
<td>With ACOG criteria Low risk (0 factors) 0.6% High risk 4% With ADA criteria Low risk 0.5% High risk 2.9%</td>
<td>ACOG criteria 11% ADA criteria 3%</td>
<td>The low prevalence of GDM observed in the low-risk group suggests that selective screening is desirable if criteria are selected to define risks</td>
<td></td>
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<tr>
<td>Yang [65] 2002, China</td>
<td>Prospective cohort N = 9741 75 g OGTT WHO criteria</td>
<td>1.8%</td>
<td>Age ≥ 25, BMI ≥ 25, family history diabetes 24%</td>
<td>Low risk 0.9%</td>
<td>12%</td>
<td>If selective screening considered in this population, age and BMI limits should be reconsidered</td>
<td></td>
<td></td>
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<tr>
<td>Jensen [54] 2003, Denmark</td>
<td>Prospective cohort N = 5235 75 g OGTT Fasting glycaemia ≥ 6.1 mmol/L (1.11 g/L) or glycaemia 2 h ≥ 9 mmol/L (1.64 g/L)</td>
<td>2.4%</td>
<td>Glycosuria, history GDM, history macrosomia (weight ≥ 4500 g), BMI ≥ 27, family history diabetes 64%</td>
<td>Population at risk 5.3% Low risk 0. %</td>
<td>7%</td>
<td>Single selective screening helps avoid a test in 2/3 of women with performance comparable to universal screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Cianni [63] 2003, Italy</td>
<td>Retrospective cohort N = 3950 100 g OGTT Carpenter &amp; Coustan criteria</td>
<td>12.3%</td>
<td>Age ≥ 25, BMI ≥ 25, family history diabetes 5.6%</td>
<td>Low risk 2.1%</td>
<td>1.5%</td>
<td>Studies on cost-efficacy ratio required before giving opinion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corcoy [62] 2004, Spain</td>
<td>Retrospective cohort N = 1635 100 g OGTT NDDG criteria</td>
<td>12.8%</td>
<td>Age ≥ 25, BMI ≥ 25, family history diabetes, personal history of abnormal glucose tolerance, unfavourable obstetrical history 7%</td>
<td>Low risk 2.4%</td>
<td>1.3%</td>
<td>Few missed GDM but too few saved screenings, making selective screening unnecessarily complex</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The performances of selective screening vary according to the population studied, the frequency of risk factors in the screened population and the thresholds used [65].

In a population of predominantly young, thin, white pregnant women considered to be at low risk for GDM, most women are not candidates for selective screening. Selective screening thus helps many women avoid having to have a test [66]. In a Spanish retrospective study [55], the prevalence of GDM in a low risk obstetrical population that represented 45% of the total population was 6 times lower (0.5%) than in the high risk population (2.9%).

Inversely, in an older, overweight obstetrical population, screening based on risk factors would probably lead to subjecting most pregnant women to screening. In North American populations where risk factors are high, selective screening could help detection in 90% of the obstetrical population [64].

### 2.2.3.2. Feasibility

Universal screening is theoretically easier than selective screening. A screening test that is too complex and based on an exhaustive list of risk factors could quickly be discontinued or only save a small percentage of the population from unnecessary tests and be of little interest in terms of a cost-effectiveness ratio.

However, a two-part universal screening (O’ Sullivan test followed by a 100 g dose of glucose if results are positive) is constraining and could delay diagnosis and care [66]. Two regional practical enquiries carried out in France five years after the recommendations for universal screening for GDM, show insufficient screening [67-69].

The main limit to a selective approach is its complexity. Nevertheless, maternal age, BMI, a history of GDM or of macrosomia are data that are easily available during the first prenatal consultation [48]. Ethnic origin is slightly more delicate to use in practice (parents of mixed backgrounds, birthplace, etc.).

### 2.2.3.3. Benefits for complications

In a Canadian retrospective registry study (NP4) on 1,729,225 women, among whom 38,274 had GDM, Wen et al. [44] concluded that the increase in the prevalence of GDM

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Diagnostic criteria</th>
<th>Prevalence of GDM in the total population</th>
<th>Selection criteria for the population at risk % population exempt if screening selective for risk</th>
<th>Prevalence of GDM in the population at risk</th>
<th>Proportion of GDM missed by selective screening</th>
<th>Authors’ conclusions on selective screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin [60] 2000, Ireland</td>
<td>Prospective randomized trial</td>
<td>N = 1853 selective screening N = 1299 universal screening 100 g OGTT NDDG criteria</td>
<td>2.7%</td>
<td>Weight &gt; 100 kg 1° degree history diabetes History macrosomia &gt; 4.5 kg History GDM History unexplained fetal death History major congenital deformities Current pregnancy: glycosuria, macromasia, hydramnios 86%</td>
<td>1.45%</td>
<td>46%</td>
<td>Universal screening better than selective screening in this Irish population</td>
<td></td>
</tr>
<tr>
<td>Cosson [61] 2006, France</td>
<td>Comparative retrospective</td>
<td>N = 1909 selective screening N = 2111 universal screening 75 g OGTT Fasting glycaemia &gt; 5.3 mmol/L (0.95 g/L) or glycaemia 2 h &gt; 7.8 mmol/L (1.40 g/L)</td>
<td>12.6%</td>
<td>Age &gt; 35 BMI &gt; 27 Personal or family history glucose intolerance or diabetes History macrosomia History GDM, preeclampsia History in utero fetal demise History congenital deformity Current pregnancy: glycosuria, macromasia, hypertension</td>
<td>8.3%</td>
<td>34%</td>
<td>Universal screening could reduce time needed to make diagnosis and begin treatment, it is associated with a better fetal prognosis</td>
<td></td>
</tr>
<tr>
<td>Chevalier [57] 2009, France</td>
<td>Prospective cohort</td>
<td>N = 2014 75 g OGTT Fasting glycaemia &gt; 5.3 mmol/L (0.95 g/L) or glycaemia 2 h &gt; 7.8 mmol/L (1.40 g/L)</td>
<td>7.78%</td>
<td>BMI &gt; 27, personal history GDM, macromasia or IUFD family history diabetes, obesity 20%</td>
<td>20%</td>
<td>34%</td>
<td>The impact of universal screening associated with intensive therapeutic care in women with no risk factor needs to be specified</td>
<td></td>
</tr>
</tbody>
</table>
was linked to the establishment of a universal screening policy: 0.3 vs. 2.7% and they suggested that cases diagnosed with universal screening were less severe than those diagnosed with selective screening. The authors compared two regions with different screening practices. In the region with universal screening, the prevalence (2.2%) of GDM was higher than where screening was selective (1%), but the frequency of perinatal complications was the same for macrosomia, hydramnios, preeclampsia and Caesareans, suggesting that universal screening had no obvious benefit in the incidence of complications related to GDM.

In a randomized prospective study (EL3) comparing selective and universal screening [60], Griffin et al. reported a significant increase in the prevalence of GDM with universal screening (2.7% vs. 1.45%). They also reported that universal screening helped make an earlier diagnosis: 30 ± 2.6 WG vs. 33 ± 3.7, but the strategy used was the screening defined in their protocol (screening at 32 WG in the risk factor group and 26-28 WG in the universal screening group). Universal screening was associated with a lower prevalence of macrosomia, Caesarean, prematurity, preeclampsia and admission in neonatal wards. The risk factors selected in this study were unusual, such as weighing over 100 kg instead of using the BMI, thus excluding a high proportion of women at risk in cases of selective screening. In a retrospective study, Cosson et al. compared over time a cohort of women who had undergone selective screening and a cohort of women who had undergone universal screening (EL4) [58]. The women did not differ in their demographic, ethnic, BMI or GDM risk factor data. The authors report rates of neonatal complications (macrosomia, prematurity before 37 WG, jaundice and transfer) lower than in the population of diabetics from the second period (universal screening) compared to that of the first period (selective screening). They suggest that universal screening could have a beneficial effect by reducing diagnosis and treatment times. A higher prevalence of GDM should be noted in this study (8.3% with selective screening, 12.6% with universal screening) and a population of diverse ethnic origins, predominately foreign: North African (24%), African (23%), Asian (3.5%), and Indian (3.7%). Data on glycaemic control was unknown. The differences in the results observed could be due to the fact that diabetes detected with universal screening is less severe. The same authors reported that neonatal and maternal prognoses of women with GDM were influenced by the presence of risk factors (family history of diabetes, BMI > 27 kg/m², age > 35 years, history of GDM, preeclampsia, macrosomia and in utero foetal demise). The presence of risk factors exposed patients with GDM to a higher risk of in utero foetal demise and a low Apgar score at birth. In the absence of risk factors, the prognosis was similar to that for women without GDM [61].

In the prospective study by Chevalier et al. [68] on 2,014 women in the south west of France who underwent universal screening with the 75 g OGTT (GDM defined as fasting glycaemia > 0.95 g/L and/or glycaemia at 2 h > 1.40), the prevalence of GDM was 7.8% and 34% of the women had no GDM risk factor, defined as: BMI > 27 kg/m², personal history of GDM, macrosomia or IUFD, family history of diabetes and obesity. In the group with no risk factors, intensive treatment was associated with a rate of macrosomia (birth weight > 90th percentile) of 3.4% and a rate of hypotrophia (birth weight < 10th percentile) of 20% vs., respectively, 10% and 13.3% in the GDM group with risk factors. It was the only study that reported an association between treatment and neonatal hypotrophia in patients with a low risk for GDM.

### 2.2.3.4. Cost-effectiveness analysis

We could not find any studies with a high level of proof that analyzed cost-effectiveness ratios for universal and selective screening.

In an Italian retrospective study by Di Cianni et al. that compared a group of 1,338 women who had undergone universal screening and a group of 4,035 women screened for risk factors, the cost-effectiveness ratio for universal screening was considered to be favourable [70]. There was however a major bias in the universal screening group receiving intensive treatment and the selective screening group receiving a conventional treatment (EL4).

In a prospective French study (EL2) carried out in 1999 on 120 women, Poncet et al. compared three screening strategies [71]:

- screening for risk factors (50 g glucose then 100 g OGTT for diagnostic purposes). The risk factors selected were as follows: first degree history of diabetes, age > 35 years, BMI > 27 kg/m², history of GDM, preeclampsia or macrosomia in a previous pregnancy;
- 2 step universal screening (50 g then 100 g OGTT for diagnostic purposes);
- 1 step universal screening (75 g OGTT).

The screening strategy for risk factors had the most favourable cost-effectiveness ratio.

Compared to selective screening, a two-step universal screening multiplied costs by 1.1 and the single step universal screening by between 3.27 and 3.75 for an avoided complication (macrosomia, prematurity, perinatal mortality or hypertension).

- **Overall, ideally, the screening strategy selected should help identify women at high risk for pathological events who would best benefit from intensive medical care and preserve others from the burden of excessive intervention, which could potentially occasion anxiety or Caesareans. In pragmatic terms and in keeping with efficacy, this would help concentrate means and not disperse them.**

- **Selective screening that is too complex and based on an exhaustive list of risk factors could be discontinued by physicians. However, maternal age, 1st degree history of diabetes, BMI, history of GDM or macrosomia is data systematically recorded during the first prenatal consultation.**
• Among these risk factors, the major impact of BMI should be highlighted in the risk of onset of GDM. It is also an independent risk factor for perinatal complications (macrosomia, preeclampsia). In low-risk populations, selective screening helps avoid testing in a high number of patients. Inversely, in high-risk obstetrical populations, and particularly given the prevalence of overweight or obese women in certain regions in France, it would only save a low proportion of women and have little interest in terms of cost/effectiveness. Selective screening could also lead to missing a high number of GDM for which the prognosis remains to be evaluated.

• Universal screening is theoretically easier to organize. There is however an increase in the prevalence of GDM to take into account in estimations of health needs required for the medical care for these patients, a fortiori if the screening thresholds proposed by IADPS are selected (expected prevalence of 16 to 18% of the population). The number of unnecessary tests and the cost-effectiveness ratio of screening low-risk women for which the benefit for perinatal complications remains controversial.

3. Conclusion

The benefits of GDM screening and the resulting medical care have only been shown in patients presenting GDM risk factors (older age, high BMI, history of GDM or macrosomia and 1st degree history of diabetes). Its interest for patients with no risk factors remains controversial.

4. Conflict of interests

No conflict of interests related to the article.

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