Therapeutic management of gestational diabetes

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Abstract

Background: Maternal and perinatal complications linked to gestational diabetes mellitus could be decreased with an intensive management approach.

Aim: To assess the effect of various treatments, glycaemic targets and procedures for self-monitoring of blood glucose on the foetal and maternal prognosis.

Methods: Systematic review of literature studying the efficacy of the treatment of gestational diabetes in order to decrease maternal-foetal morbidity-mortality. Analysis based on bibliographic search in PubMed using the following keywords: “therapeutic”, “treatment” and “gestational diabetes”.

Results: Specific treatment of gestational diabetes (dietary, adapted physical activity, self-monitoring of blood glucose, insulin-therapy if appropriate) reduces severe perinatal complications (composite criterion), foetal macrosomia and preeclampsia compared to the absence of therapy, with however an increase in the number of labour inductions, and without any increase in the number of caesarean sections. Regarding oral antidiabetic agents (glibenclamide or metformin), despite the absence of difference found on foetal or maternal prognosis compared to insulin, they should not be prescribed during pregnancy at this time.

Conclusion: The treatment of “severe or moderate” gestational diabetes is recommended. Additional studies, in particular long-term studies in children, are warranted before oral antidiabetic agents can be used.

Keywords: Gestational diabetes ; Treatment ; Blood glucose ; Dietary ; Physical exercise ; Insulin ; Oral antidiabetic agents ; Review

Résumé

Prise en charge thérapeutique du diabète gestationnel ?

Contexte : Les complications maternelles et périnatales liées au DG pourraient être diminuées par une prise en charge intensive.

Objectif: Évaluer l’effet des différents traitements, les objectifs glycémiques, et les modalités d’autosurveillance glycémique sur le pronostic foetal et maternel.


Résultats: Le traitement spécifique du DG (diététique, activité physique adaptée, autocontrôle glycémique, insulinothérapie si indiquée) réduit les complications périnatales sévères (critère composite), la macrosomie foetale, et la prééclampsia par rapport à l’abstention thérapeutique, avec cependant une augmentation du nombre de déclenchements, sans augmentation du nombre de césariennes. Concernant les antidiabétiques oraux (glibenclamide ou metformine), malgré l’absence de différence sur le pronostic foetal ou maternel lorsque comparés à l’insuline, ils ne sont pas à ce jour indiqués durant la grossesse.

Conclusion. Le traitement du DG « sévère ou modéré » est indiqué. Des études complémentaires notamment à long terme chez l’enfant sont nécessaires, avant de pouvoir utiliser les antidiabétiques oraux. gestationnel.

La recherche d’un diabète gestationnel, indépendamment de la politique de dépistage recommandée, doit être pratiquée entre
Introduction

The therapeutic interventions will be studied by distinguishing lifestyle measures on one hand, including diet and physical activity, from drug interventions on the other (insulin and oral antidiabetic agents). We will not explore the specific interventions related to obstetrical management here.

All of these therapeutic interventions aim to maintain glucose levels as close as possible to those of non-diabetic pregnant patients in order to significantly reduce the maternal-foetal morbidity and mortality.

Material and methods

The literature search was performed systematically with the Medline and Cochrane Library computerised databanks for studies published between 1966 and May 2010; it was completed with a manual search from bibliographies of reviews. The reviews from The French National Authority for Health (HAS) 2005, the US Preventive Services Task Force 2008, Cochrane 2009, NICE 2008, the recommendations of the 5th consensus on GDM 2007 and summary reviews were consulted. The goal of the research was to evaluate the effect of different forms of therapeutic management on the maternal-foetal prognosis in gestational diabetes. Randomised, controlled studies and meta-analyses were considered when they existed, but non-randomised, controlled studies, cohort studies and case-control studies were used in addition.

The keywords used were: gestational diabetes, treatment, self-monitoring of blood glucose, blood glucose, dietary, caloric restriction, fibre, glycaemic index, physical exercise, therapy, insulin, insulin analogue, oral antidiabetic agents, oral antihyperglycaemic agents, glibenclamide, glyburide, metformin, CSII.

Only publications in English or in French were selected.

2.1. Determination of the glycaemic targets

The definition of the glycaemic target in the management of gestational diabetes mellitus (GDM) remains controversial. The objective is to obtain a glycaemia as close to normal as possible in order to reduce the risk of macrosomia and its consequences. The recommendations of different scientific societies suggest a fasting plasma glucose between 0.90 and 1.05 g/L (4.95-5.8 mmol/L), a 1-hour postprandial plasma glucose less than 1.40 or 1.30 g/L (7.7 or 7.15 mmol/L), or a 2-hour postprandial plasma glucose less than 1.20 g/L (6.6 mmol/L) [1].

There are no randomised studies or meta-analyses comparing these different glycaemic thresholds in the treatment of GDM. Data from the literature confirms the thresholds used in France based on the following: the concept of normal glycaemia during pregnancy, observational studies showing a positive correlation between the glycaemic level, macrosomia and its consequences, and randomised studies of therapeutic intervention.

The facts of pathophysiology (maternal hyperglycaemia inducing foetal macrosomia per hyperinsulinaemia) prompt care to centre on the “normalisation” of glycaemia levels in hope of restoring the macrosomia rate to the values of the general population.

Normal glycaemic levels during pregnancy were investigated in three studies. In the study by Yogev et al., the glycaemic profile of 57 non-diabetic women who had normal weight (n = 42) or were obese (BMI ≥ 27.3, n = 15) was obtained through continuous measurement of glycaemia. The mean value of the fasting glycaemia was 0.75 g/L (± 0.12) (4.1 ± 0.66 mmol/L), without any differences between the two

groups, while the glycaemic peak in the postprandial period was higher and occurred later in the obese women: 1.17 ± 0.08 g/L (6.4 ± 0.44 mmol/L) versus 1.06 ± 0.16 g/L (5.8 ± 0.88 mmol/L) (p = 0.04), and at 71 ± 30 versus 78 ± 31 minutes (p = 0.03) [2]. In 51 Caucasian, non-obese women between 28 and 30 weeks gestation, Parretti et al. reported a mean glycaemia in the third trimester of 0.75 ± 0.05 g/L (4.1 ± 0.27 mmol/L) [3]. In 32 pregnant, Caucasian, non-obese (mean BMI 22) women, Siegmund et al. showed a relatively stable fasting plasma glucose at different points in the pregnancy: 0.79 ± 0.072 g/L (4.4 ± 0.4 mmol/L) at 16 weeks gestation, and 0.79 ± 0.09 g/L (4.4 ± 0.5 mmol/L) at 32 weeks gestation. They also showed a mean postprandial glycaemia (time not specified) of 0.95 ± 0.11 g/L (5.31 ± 0.6 mmol/L) at 16 weeks gestation, and 1.10 ± 0.12 g/L (6.14 ± 0.7 mmol/L) at 32 weeks per continuous glucose monitoring (CGMS) over three days and OGTT 75 g [4].

The cohort studies show that the lower the glycaemia, particularly the postprandial glycaemia, the more the rate of maternal-foetal complications decreases. In the MiG (Metformin in Gestational Diabetes) randomised study comparing metformin to insulin in 750 women presenting with GDM that was insufficiently controlled with dietary measures, the results of capillary glucose testing in two groups were pooled and separated into tertiles. The patients with fasting capillary glucose less than 0.89 g/L (4.9 mmol/L) and/or a 2-hour postprandial glucose level between 1.07 (5.9 mmol/L) and 1.16 g/L (6.4 mmol/L) had a significantly lower rate of complications than those with a fasting glucose ≥ 0.89 g/L (4.9 mmol/L) and/or a postprandial glycaemia ≥ 1.16 g/L (6.4 mmol/L). The fasting capillary glucose was significantly correlated with neonatal complications (hypoglycaemia, respiratory distress, phototherapy, birth trauma, a 5-minute Apgar score < 7 and prematurity), and the postprandial glucose was significantly correlated with preeclampsia and birth weight greater than the 90th percentile [5] (EL2). In a prospective study of 334 women with GDM who performed seven capillary glucose checks per day in the third trimester, Langer et al. demonstrated that a mean capillary glucose level less than 0.87 g/L was associated with a low rate of birth weight greater than the 90th percentile (1.4 %) but also with an increased frequency of birth weight lower than the 10th percentile (20 %). However, the frequency of birth weight greater than the 90th percentile was 24 % when the mean glycaemia level was more than 1.05 g/L. Compared to a control group of 334 women matched for obesity, ethnicity and parity, women presenting with a mean glycaemia level between 0.87 and 1.04 g/L had a comparable rate of birth weights greater than the 90th percentile (12 %) and less than the 10th percentile (11 %) [6] (EL2).

Two randomised studies showed that the management of GDM (glycaemic targets defined) compared to the lack of management resulted in a reduction of maternal-foetal morbidity [7, 8]. The randomised and multicentre ACHOIS study by Crowther et al. [7] included 1000 women that had a positive screening glucose challenge test [1-hour blood glucose level after 50 g of glucose greater than 1.40 g/L (7.7 mmol/L) or at least one risk factor for gestational diabetes, and a 75 g OGTT, done between 24 and 34 weeks gestation, a fasting plasma glucose less than 1.40 g/L (7.7 mmol/L) and a 2-hour blood glucose level between 1.40 and 2 g/L (7.7 and 11 mmol/L). The treatment in the management group included a diet order, which was established after an individual interview (adapted according to the pre-pregnancy weight, the weight gain during pregnancy, the food survey and the level of activity) and capillary self-monitoring of blood glucose four times per day for 15 days, then once daily if the glycaemic targets are met. The glycaemic targets were fasting plasma glucose between 0.63 g/L (3.5 mmol/L) and 0.99 g/L (5.5 mmol/L), preprandial glucose less than 0.99 g/L (5.5 mmol/L) and 2-hour postprandial glucose less than 1.26 g/L (7 mmol/L). Treatment with insulin was started if two fasting or postprandial blood glucose readings exceeded the cited thresholds [from 35 weeks gestation the threshold for the postprandial glycaemia was 1.40 g/L (8 mmol/L) or one postprandial glycaemia greater than 1.62 g/L (9 mmol/L) over a monitoring period of 15 days. The women in the control group as well as the medical team were not aware of the diagnosis of gestational diabetes. The characteristics of the women from both groups were similar with regard to age (30.9 ± 5.4 versus 30.1 ± 5.5 years), median BMI (26.8 (23.3-31.2) versus 26 (22.9-30.9) kg/m²) and ethnicity (Caucasian 73 % versus 78 %). Composite endpoints were used (death, shoulder dystocia, fracture, paralysis) and were significantly reduced (4 % versus 1 %, P < 0.05); the rate of macrosomia and birth weight greater than the 90th percentile was also significantly reduced (10 % versus 21 %; and 13 % versus 22 % p < 0.001). The rate for caesarean delivery (31 versus 32 %, ns) was identical; however the rate of labour induction was significantly increased in the management group (39 % versus 29 %, p < 0.03), as were admissions to the neonatology unit (71 % versus 61 %; p = 0.04). In this study there was no information on the glycaemic profiles obtained from the management group of women, but 20 % were being treated with insulin. There was bias in the control group in which slightly less than 20 % of women had normal results from the 75 g oral glucose tolerance test (OGTT), and 10 % of the control group were treated with insulin. The significantly increased number of labour inductions in the management group could have an influence on the reduction in macrosomia and complications. The randomised and multicentre NICHD study by Landon et al. [8] included 958 women that had a positive 50 g tolerance test (1-hour glucose between 1.35 and 2.00 g/L; 7.5 and 11 mmol/L) between 24 and 30 weeks gestation; they also had a 100 g OGTT in which the fasting plasma glucose was less than 0.95 g/L (5.3 mmol/L) and at least two blood glucose levels greater than 1.80 g/L (10 mmol/L) at 1 hour, 1.55 g/L (8.6 mmol/L) at 2 hours or 1.40 g/L (7.7 mmol/L) at 3 hours. The treatment in the management group included dietary measures, self-monitoring of blood glucose (fasting and 2-hour postprandial), and insulin if the targets were not
reached during the monitoring. The glycaemic targets were a fasting plasma glucose less than 0.95 g/L (5.3 mmol/L) and 2-hour postprandial glucose less than 1.20 g/L (6.7 mmol/L). The characteristics of the women in both groups were similar with regard to age (29.2 ± 5.7 versus 28.9 ± 5.6 years), mean BMI (30.1 ± 5 versus 30.2 ± 5.1 kg/m²), and ethnicity (Hispanic 57.9 % versus 56 %, Caucasian 25.4 % versus 25.2 %). The women treated by diet or insulin achieved the fasting glycaemic and postprandial targets; the glycaemic profile was obtained using the memory of the glucose meters. The primary endpoint was negative (composite endpoint: stillbirth and neonatal death, hypoglycaemia, hyperbilirubinaemia, neonatal hyperinsulinaemia, birth trauma). With regard to the secondary endpoints, which were specified before the study, the frequency of weight over 4 kg was decreased in the management group (5.9 versus 14.5 %; \( p < 0.001 \)), as was the frequency of the birth weight greater than the 90th percentile. The rate of caesarean delivery was decreased in the management group (26.9 versus 33.8 %; \( p = 0.02 \)). There were no differences noted with regard to rate of birth weight less than the 10th percentile, prematurity, the rate of labour induction, admissions to the neonatology unit or hypoglycaemia requiring intravenous treatment.

Both of these studies, which have different glycaemic targets, show the benefit of management for gestational diabetes. In the NICHD study, the management of gestational diabetes, even if moderate, significantly reduced the incidence of macrosomia, even though the study lacked the statistical power to demonstrate a benefit regarding the complications related to macrosomia.

2.2. Benefit of self-monitoring of blood glucose in the management of gestational diabetes

Self-monitoring of blood glucose (SMBG) is one of the measure of management of GDM, but the level of proof in the literature is still not sufficient enough for demonstrating its benefit. There is no consensus concerning the modalities of SMBG (frequency, timing, duration). Nevertheless, SMBG allows women to adjust their diets and helps the medical team in the decision-making regarding the use of insulin. When women are treated with insulin, the SMBG is essential for adjusting the insulin dose.

2.2.1. Benefits of SMBG

There have been small, non-randomised, case-controlled or retrospective studies showing a decreased rate of macrosomia in patients performing SMBG (EL4). One retrospective study comparing 315 women using SMBG done four times daily (before meals and at bedtime) to a historic cohort of 675 women monitored weekly by an office-based venous test showed a decreased incidence of macrosomia (29.5 % versus 21.9 %, \( p = 0.013 \)) in the SMBG group [13] (EL4). One case-control study matched for age, parity, weight and height on 116 women comparing SMBG (fasting and one hour after meals) to a weekly office-based testing showed significantly decreased rates of macrosomia (birth weight > 4 kg) and large-for-gestational-age children (respectively, 9 % versus 24 %, \( p < 0.05 \); and 12 % versus 41 %, \( p < 0.05 \)). The women in the SMBG group had been significantly treated more often with insulin (50 % versus 21 %, \( p < 0.01 \)) [14] (EL3).

The randomised studies based only on SMBG were not able to show a benefit, but they had limitations, especially an insufficient number of patients for assessing the perinatal events or methodological biases. Seventy women who had been screened by OGTT were randomised: SMBG (5 times per week, 1 or 2 hours after meals, target < 1.26 g/L (6.9 mmol/L), or no monitoring. No differences with regard to macrosomia...
and admission into the neonatal intensive care unit were found. The frequency of the SMBG was however low and the statistical power of the study was insufficient [15] (EL4).

One randomised study on 300 women (monitoring reinforced with SMBG versus “ordinary” monitoring) did not show a reduced frequency of macrosomia (defined by a birth weight > 4.5 kg) or of perinatal events. Although the women in the SMBG group had been significantly more often treated with insulin (24% versus 10%), several methodological limitations of this study did not enable it to draw conclusions. These included access of the control group to SMBG, and the fact that 10.6% of women in the control group had been treated from the beginning with insulin and were considered to be type 1 or 2 diabetes. The definition of macrosomia (BW > 4.5 kg), as well as the fasting glucose target (0.80 g/L (4.4 mmol/L) were not the most commonly used in the studies [16] (EL3).

The authors of these two cases concluded that there was a need for a large complementary randomised study.

SMBG was included as part of the management treatment of GDM in the randomised interventional studies that exhibited a benefit.

2.3. Frequency of SMBG

There is great diversity in the practice of SMBG, ranging from a performance of 4 to 7 blood glucose checks per day. The studies with SMBG have diverse targets and endpoints, thus preventing any conclusions from being drawn [12, 17, 18]. The randomised study of De Veciana et al., which is traditionally cited and compares the adjustment of insulin according to the preprandial or postprandial glycaemia, cannot be used for gestational diabetes, as the included patients had type 2 diabetes [17]. In the two interventional studies [7, 8], the SMBG protocol consisted of 4 capillary fasting blood glucose checks per day, and 2-hour postprandial checks. The monitoring was reduced in the ACHOIS study if the glycaemia results were within the target range during the 15-day monitoring period [7].

2.4. Choice of device for self-monitoring of blood glucose

The choice of device should technically take into account the characteristics of the reagent strips (haematocrit range compatible with pregnancy) and include accessible memories. The devices must comply with the NF EN ISO 15197 standard, as this standard ensures an acceptable level of performance of these systems, even if for the “accuracy” parameter the HAS work group considers the acceptable margin of error to be wide (20%). A 5% margin of error, as supported by the American Diabetes Association (ADA), seems difficult to impose; a 15% margin of error would be more acceptable [19]. These devices have a validity of four years and must be calibrated according to the current procedures.

2.4.1. Conclusion

SMBG is recommended in the treatment of GDM, even if the level of proof is low. It makes up part of a comprehensive management plan enabling diet adjustment, and is an aid for monitoring and for decision-making concerning the start of insulin treatment. The glycaemic targets are an educative tool for diet comprehension. Patient education is essential for ensuring the quality of the self-monitoring procedure. The level of proof is still insufficient for determining the frequency (between 4 and 6 days) and the duration of SMBG during GDM treated with diet alone.

3. Dietary management

Dietary management is the cornerstone of GDM treatment, as it enables optimal glycaemic control to be attained. It must be planned as part of the dietary education based on the specific nutritional needs of pregnancy and centred on the dietary survey and the knowledge of the patients (habits, traditions, customs). It must take into account the weight before pregnancy and the weight gain during pregnancy. In the beginning of pregnancy, the energy needs of pregnant women without GDM and with a normal pregestational BMI are between 2200 and 2800 kcal/day, i.e., 30 to 35 kcal/kg/day; this increases in the second and third trimesters by 250 to 300 kcal/day [20].

3.1. Is there a benefit in fractionating glucose intake?

The goal of fractionating food intake into three meals and two to three snacks is to distribute the glucose intake throughout the day in order to control the postprandial glucose, while at the same time maintaining a satisfactory nutritional intake. The evening snack decreases the night time ketogenesis related to fasting. These pragmatic recommendations are old and are defined empirically, but they have met the general approval of the different scientific societies. There have been no randomised studies done on the fractionating of food intake during GDM.

3.2. What should be the proportion of carbohydrate intake out of the total calorie intake?

The percentage of recommended glucose in the total calorie intake is between 40% and 50% [9, 21]. There are studies showing the influence of the proportion of carbohydrates during meals on postprandial glycaemia, but there are only a few, and they have small samples and do not perform an assessment of perinatal events.

Perterson et al. showed in 14 women that in order to obtain a 1-hour blood glucose after meals less than 1.40 g/L (7.7 mmol/L), the percentage of carbohydrates must be 45%
at breakfast, 55 % at lunch and 50 % at dinner; to obtain a blood glucose < 1.20 g/L (6.6 mmol/L), this distribution must be 33 %, 45 % and 40 %, respectively [22] (EL3).

Major et al. compared women with GDM at 24 – 28 weeks gestation that had a low (< 42% of total caloric intake) or a high (> 45%) carbohydrate ration. With less than 42 % carbohydrates, the postprandial blood glucose was lower (1.10 versus 1.32 g/L, p < 0.04), there was less need for insulin (4.7 % versus 33 %, p = 0.047), and the rate of large-for-gestational-age infants and the rate of caesarean delivery for macrosomia were significantly lower (9 % versus 42 %, p < 0.035; and 3 % versus 48 %, p < 0.037) [23].

3.3. Benefit of carbohydrates with a low glycaemic index ?

Few studies have focused on the benefit of carbohydrates with a low glycaemic index (GI). Their consumption may result in: 1) a reduction in postprandial glycaemic excursion compared to carbohydrates with a high GI (observational non-randomised study in 14 non-pregnant women and 12 pregnant women without GDM (EL4) [24]; 2) a 30 % reduction in the need for insulin (63 randomised women with GDM comparing two types of carbohydrate intake (175 g of carbohydrates with low or high GI) [25]; and 3) a significant reduction in birth weight and an increase of small-for-gestational-age infants in women without gestational diabetes [24, 26, 27] (EL4).

There has been no randomised study done with sufficient sample size to draw a conclusion as to the benefits of carbohydrates with a low GI. It seems pragmatic to advise women with GDM to avoid or reduce carbohydrate foods that cause postprandial hyperglycaemia, which vary amongst individuals. The elimination of carbohydrates with a very high glycaemic index (soda, sugar, sweets, etc.) also seems pragmatic. The practice of self-monitoring of blood glucose guides the women in the choice of carbohydrate foods.

3.4. Benefit of fibre intake

The use of fibre is traditionally recommended with GDM, as it may reduce the postprandial blood glucose. An intake poor in fibre (10 g per day) [28] decreased the insulin sensitivity in the third trimester in 14 women without GDM. The postprandial secretion of insulin is also reduced with a diet rich in fibre (50 g/day) in non-diabetic women in the second trimester of pregnancy [29]. These studies however were done with small sample sizes of women and without GDM (EL4).

There is no proof that fibre intake is beneficial in the diet during GDM (EL4).

3.5. What caloric restriction should overweight or obese patients follow?

Caloric restriction in obese patients presenting with GDM improves the glycaemic control and reduces weight gain. The ACHOIS and NICHD studies showed the effect of diet on the limitation of weight gain. There are very few studies on caloric restriction in GDM, and those that exist are often old with small sample sizes and not all of them are randomised.

Algert et al. showed that a calorie restriction (1700-1800 kcal/day) in obese women (BMI > 27) resulted in a lower weight gain without leading to ketonuria, even with 1500 kcal/day [30].

In a case-controlled study of 35 women with GDM, Donhorst et al. showed that a calorie restriction (1200-1800 cal/day) entailing a 30 % reduction from their prenatal calorie intake results in a comparable rate of children with birth weights greater than 4 kg compared to a population of women without GDM, and without an increase in the number of small-for-gestational-age infants. The sample size of this study however was small (EL3) [31].

Knopp et al. showed that a 50 % reduction in calorie intake in obese women with GDM leads to glycaemic improvement, which was identical to a 33 % reduction but resulting in ketonuria [32]. The presence of ketonaemia is more common in women with GDM than those without, especially if they have a calorie restriction [33]. The impact of ketogenesis on foetal development during GDM remains controversial. One case-control study showed a link between ketonuria/ketonaemia in the third trimester of pregnancy and a mental developmental deficit in children at 5 years [34]. This study is regularly cited to justify the limitation of calorie restriction. A 30 % restriction of estimated caloric intake enables ketonuria or an increase in free fatty acids to be avoided [35] while improving glycaemic control at the same time. A more severe calorie restriction in obese women presenting with GDM is not recommended. Apart from a period of fasting (nocturnal fasting, for instance), the persistence of ketonuria in women that have not gained weight or are losing weight should signal a calorie restriction that is too severe (expert opinion).

The calorie intake in obese women presenting with gestational diabetes is a minimum of 25 cal/kg/day, calculated from the pre-pregnancy weight without going below 1500 kcal/day.

4. Physical activity

The practice of regular physical activity (PA) improves insulin sensitivity and is recommended during pregnancy. Few studies have been done on the benefits of PA in GDM, and they have had small sample sizes and low level of proof. A meta-analysis by Cochrane in 2006 [36] selected four trials that had been performed on 114 women [37, 38, 39, 40]. No benefit with regard to maternal-foetal complications could be demonstrated, perhaps due to the heterogeneity of the studied criteria and the insufficient size of these studies (EL1).

A randomised study on 19 women compared a diet program alone to one combined with regular PA (20 min, 3 times a week). At 6 weeks, the HbA1c had decreased significantly (4.2 % ± 0.2 % versus 4.7 % ± 0.2 %, p < 0.001), as had the fasting plasma glucose (0.70 (3.8 mmol/L) versus 0.87 g/L (4.8 mmol/L) and the
1-hour postprandial glucose (1.07 (5.9 mmol/L) versus 1.89 g/L (10.4 mmol/L), \( p < 0.001 \)) [37] (EL2).

One randomised study on 33 women did not show a difference in glycaemic control [38] (EL2).

One randomised study on 32 women compared a diet program alone to one combined with regular physical activity (30 min, 3 times a week). In the PA group, the need for insulin only decreased in women with a prepregnant BMI > 25. The insulin doses were smaller and the postprandial glucose was significantly lower. But the pre-pregnancy weights were different, making it difficult to interpret the results [39] (EL2).

One randomised study (41 women requiring insulin therapy) showed that a combination of PA and diet compared to diet and insulin resulted in good glycaemic control without the need for insulin for 17 women out of 21 [40] (EL2).

One randomised cross-over study compared fasting glucose to the glucose level after a breakfast that included 20 g of carbohydrates followed by either one hour of activity or one hour of rest in 20 women with GDM. The post-exercise glucose level decreased (0.97 g/L versus 1.09 g/L), but there was no observable difference seen in the 2-hour glucose level [41] (EL4).

Physical activity makes up part of a more comprehensive management program. The studies lack statistical power to be able to conclude whether physical activity alone has an effect on perinatal events. Nevertheless, regular PA plays a role in improving postprandial glycaemia, reducing the need to add insulin (expert advice).

A regular activity of 30 minutes performed 3 to 5 times per week is recommended with the approval of an obstetrician (expert advice).

5. **Insulin**

Insulin is the only drug treatment for hyperglycaemia that is currently validated in pregnancy, as it does not cross the placenta. The use of human insulin (regular or intermediate insulin) over many years has enabled the experts to consider this as proof of its safety during pregnancy (EL3).

5.1. **What regimen should be used?**

5.1.1. **Intensified regimen**

A single randomised study compared two insulin therapy regimens in patients with GDM [12]: 138 patients received an “intensified treatment” (diet + 3 injections of preprandial regular insulin and an injection of intermediate insulin at bedtime), and 136 patients followed a diet + 2 injections per day (2 mixtures of insulin). The results in the “intensified treatment” group showed better glycaemic control [HbA1c 5.5 % versus 5.8 % (± 0.3 %; CI 95 %, - 0.2 % to 0.4 %)], and a significant reduction in morbidity [RR 0.59, (CI 0.38-0.97)], neonatal hypoglycaemia risk [RR 0.12 (0.05, 0.29)], macrosomia [52, 53, 55, 58]. There were no significant differences in macrosomia, Apgar score, obstetrical trauma, caesarean rate or in intrauterine growth restriction (IUGR).

**An intensified insulin regimen provides better glycaemic control without harmful effects on the maternal-fœtal prognosis (EL2).**

5.1.2. **Subcutaneous insulin infusion pump**

One case-control study [43] compared 30 patients, 20 of whom had GDM, who used a pump for treatment to 60 patients matched with respect to ethnic origin and type of diabetes. This study however was not contributory to GDM due to its small sample size and its mainly Polynesian population with major insulin resistance.

**The current data are insufficient for evaluating the treatment with a pump in GDM.**

5.2. **What insulin should be used?**

5.2.1. **Rapid-acting insulin analogs**

**Lispro**

The results were analysed in two recent reviews [44, 45] and one meta-analysis [46].

Animal studies showed no teratogenic or harmful effect on fertility [47]. Lispro insulin has a homology with the IGF-1 receptor that is greater than that of human insulin [48]. It does not cross the placenta at the usual doses used in clinical practice [49, 50].

No randomised control study of more than 100 patients has been done. A retrospective study in pre-existing diabetes (533 patients treated with lispro before conception and during their first trimester) did not find an increased rate of congenital malformations [51] (EL3).

One randomised study [52] and two retrospective studies [53, 54] in GDM compared the rates of congenital malformations and spontaneous miscarriage while using lispro (111 patients) and regular insulin (197 patients), with no significant difference found between the two groups (EL3). Better glycaemic control was obtained with regard to HbA1c [53, 54] and postprandial glucose [55, 56]. The area under the curve for blood levels of glucose and insulin and the C-peptide rate were lower after a test meal with lispro insulin than with regular insulin [52] (EL1). The difference with regard to HbA1C was not confirmed in the meta-analysis by Sumeet [46]. The data were not conclusive for the two studies that compared hypoglycaemia [52, 56]. Satisfaction and compliance were better using lispro (111 patients) and regular insulin (197 patients), with no significant difference found between the two groups (EL3). Better glycaemic control was obtained with regard to HbA1c [53, 54] and postprandial glucose [55, 56]. The area under the curve for blood levels of glucose and insulin and the C-peptide rate were lower after a test meal with lispro insulin than with regular insulin [52] (EL1). The difference with regard to HbA1C was not confirmed in the meta-analysis by Sumeet [46]. The data were not conclusive for the two studies that compared hypoglycaemia [52, 56]. Satisfaction and compliance were better using lispro [54, 57]. There was no difference seen in the maternal-fœtal prognosis with regard to gestation at delivery, and the rates of preeclampsia, caesarean and macrosomia [52, 53, 55, 58].

**Aspart**

This rapid-acting analog has a comparable affinity to
similar to human insulin [48]. The efficacy of aspart in GDM is comparable to that of regular insulin, with better postprandial control (studies in 15 and 27 women) [59, 60].

A randomised, multicentre study in type 1 diabetes compared aspart and regular insulin and showed comparable glycaemic control with regard to HbA1c; the result was better however at the end of the 1st trimester and the end of the 3rd trimester for the mean postprandial glycaemic values. The difference was not significant with regard to severe or nocturnal hypoglycaemia [61]. The foetal prognosis was comparable in both groups, with a more favourable trend for the aspart group: less foetal loss and premature delivery. The mean gestational age was similar [62].

Gluulisine
There is not sufficient data concerning the use of glulisine insulin during pregnancy [63].

5.2.2. Long-lasting insulin analogs

Glargine and detemir insulins do not currently have an MA during pregnancy.

Glargine
Animal studies have not shown teratogenic or harmful effects on fertility, but there is an increased risk of abortion, with a probable role of hypoglycaemia caused by high doses of insulin [64]. This harmful role of hypoglycaemia has however never been confirmed in humans.

The affinity to the IGF-1 receptor is increased, suggesting a mitogenic risk [65, 48], which has not been confirmed in subsequent animal studies [66] or in vitro studies on diabetic human muscle.

At therapeutic doses, glargine does not cross the placenta according to the ex vivo transplacental transfer method [67]. No randomized studies have been done concerning its use during pregnancy. The data are very limited and exist mainly in type 1 diabetes [68-74].

Three observational studies have been done on GDM. The first reported on the use of glargine in four pregnancies with healthy development [75]. The second case-control compared 22 women using glargine to 22 women using NPH insulin [68]. There were no differences in the preprandial glucose levels at lunch and dinner; weight gain was significantly less in the glargine group and there were no differences in the gestation at delivery and mode of delivery, birth weight or Apgar score. The 3rd study was prospective [76] and followed 56 patients with pre-existing diabetes and 82 patients with GDM who were treated with glargine or NPH from the preconceptual period to the delivery. This study concluded that there was a reduction in maternal and foetal morbidity.

Detemir
Detemir has less affinity for the IGF-1 receptor than that of human insulin [48]. The results of a randomized prospective study of detemir versus NPH in type 1 diabetes are pending.

5.3. When should insulin be started?

5.3.1. Based on glycaemic targets

Insulin therapy is indicated once the diet is not sufficient for maintaining the glycaemic targets (see Chapter 1 Glycaemic targets). The following paragraph tries to assess the glycaemic thresholds that would justify the initiation of insulin therapy.

A randomised study of 202 patients did not show any benefit from insulin therapy in “moderate” diabetes (fasting glucose < 1.27 g/L (7 mmol/L) and 2-hour postprandial glucose < 1.63 g/L (9 mmol/L)) [77]. A second randomised study of 108 patients [78] showed that the mean birth weight and the rate of macrosomia were significantly reduced in the group treated with insulin versus diet alone. In addition, when the glycaemic control was not sufficient, there was an increased risk (30 %) of increased foetal growth with or without insulin.

A cohort study [79] comparing 153 women with GDM who were treated with diet and intensified glycaemic self-monitoring or by insulin when the fasting targets (< 1.05 g/L ; 5.8 mmol/L) and the postprandial targets (< 1.40 g/L ; 7.7 mmol/L) were not met (7.2 % of patients) did not find any difference in relation to a reference population (2153 non-diabetic women) with regard to birth weight of the infant and macrosomia.

The cohort study [80] (75 women) identified predictive factors of treatment with insulin, with an indication for fasting glycaemia > 0.95 g/L (5.2 mmol/L) and postprandial glycaemia > 1.25 g/L (6.9 mmol/L) ; BMI before pregnancy > 28 kg/m², early diagnosis of GDM and an increased 3-hour OGTT glycaemia.

The glycaemic thresholds of insulin indication were therefore variable between 0.95 g/L (5.2 mmol/L) and 1.27 g/L (7 mmol/L) when fasting and between 1.25 g/L (6.9 mmol/L) and 1.63 g/L (9 mmol/L) 2 hours postprandial. However, since then the recent studies of Crowther et al. [7] and Landon et al. [8] showed the benefit of therapeutic intervention using glycaemic thresholds < 0.95 g/L (5.2 mmol/L) fasting and < 1.20 g/L (6.6 mmol/L) 2 hours postprandial for the first author, and between 0.63 g/L (3.4 mmol/L) and 0.99 g/L (5.4 mmol/L) fasting and < 1.26 g/L (6.9 mmol/L) 2 hours postprandial for the second author.

The available data are reassuring concerning the safety and efficacy of the rapid-acting insulin analogs lispro and aspart during pregnancy (NP2), but they are insufficient for the routine use of long-lasting insulins, making NPH the preferred choice in this case (large clinical experience).
5.3.2. Based on ultrasound data

Five randomised studies assessed the benefit of ultrasound biometry in treatment adjustment for GDM (see text O. Thiebaugeorges). These trials were carried out on 60 to 151 women and compared the rates of macrosomia [81-85], small-size-for-gestational-age [83, 84] and neonatal complications [82, 83] according to two strategies for insulin therapy indication. One was based on ultrasound biometry and the other on glycemic objectives. No differences in the mentioned criteria were found, with both strategies being equivalent with regard to birth weight greater than the 90th percentile.

In an attempt to prevent macrosomia, a randomised trial [85] compared a single ultrasound performed at 32 weeks gestation to two ultrasounds at 28 and 32 weeks gestation. The rate of macrosomia was significantly higher in the group receiving a single ultrasound (71.1 % versus 33.3 %, p < 0.005).

Several randomised trials of low statistical power have shown that use of the abdominal circumference measurement for adjusting the treatment of GDM reduces the rate of large-for-gestational-age infants. Due to the heterogeneity of the studies however, an optimal modality of use of biometry cannot be defined and would require other larger randomised trials be done on all the GDM defined according to homogeneous criteria.

5.4. Oral antidiabetic agents

Although there is no theoretical risk of congenital malformations in GDM beginning after the period of organogenesis, anomalies in fetal programming cannot be ruled out, and despite their ease of use, oral antidiabetic agents (OAD) do not have an MA in pregnancy.

5.4.1. Glibenclamide (Glyburide)

The placentical crossing of glibenclamide has been shown to be negligible [86-88], contrary to that of the first generation sulfonylureas. No teratogenic effect has been shown in animals; there have been no reports of increased incidence of congenital defects [88]. There are only a few published data, but no malformation effect has been proven to date [89].

There is much data concerning the 2nd and 3rd trimesters (see paragraph VI.5.1). They mainly concern GDM, and no particular neonatal effect has been proven in newborns.

The data on glibenclamide appears reassuring, although additional studies are required before its routine use in pregnancy can be considered.

5.5. Metformin

Metformin crosses the placenta [87, 90], however no teratogenic effects or increase in congenital malformations have been evidenced [91]. The published data during pregnancy mainly focuses on polycystic ovary syndrome in the 1st trimester and on GDM in the 2nd and 3rd trimesters. No particular neonatal effect has been found [89]. However no randomised studies have been performed from the preconception period in diabetes.

Due to the placental crossing of metformin and the lack of sufficient data, great caution must be employed with its use.

5.6. Acarbose

Animal studies have found no teratogenic or embryotoxic effects (product information) [92]. One randomised study with a very small sample did not find any alteration in foetal prognosis [93].

5.7. Glitazones

Rosiglitazone crosses the placenta (data unknown for pioglitazone) in the first trimester of pregnancy [94]. Animal studies have demonstrated fetotoxicity [95].

5.8. What is the role of OAD?

5.8.1. Insulin/OAD comparison (glibenclamide or metformin)

More than 20 studies have been published since the year 2000, some which were randomised and showed that OAD were efficacious and were comparable to insulin with regard to glycemic targets attained and maternal-fetal prognosis (EL1).

The meta-analysis of Moretti et al. published in 2008 [96] reported on nine studies [97-104], one of which was randomised [88], for a total of 745 women treated with glibenclamide from 24 weeks gestation and 637 treated with insulin. The risk of macrosomia with glibenclamide did not increase (OR 1.07; CI 95 %, 0.78-1.47). There was no difference in birth weight (mean weighted difference : 20.46 g; CI 95 %, -34.90 to 75.82), in the incidence of large-for-gestational-age infants [OR 1.04; CI 95 % (0.75-1.43)], in gestation at delivery [mean weighted difference : 0.02 weeks, CI 95 % (0.23 to 0.26)], in the incidence of transfer to the neonatology unit [OR 0.95; CI 95 % (0.43-2.09)] or in neonatal hypoglycaemia [OR 1.24; CI 95 % (0.91-1.69)].

The review by Nicholson et al. [105] analysed 3 randomised studies on glibenclamide versus insulin (n = 478) [88, 93, 106], one randomised study on insulin versus metformin (n = 751) [107], and five observational studies (n = 831) [101-104, 108]. Twenty-four percent of patients obtained their glycemic targets...
on glibenclamide. The maternal and foetal prognoses were comparable on glibenclamide and metformin compared to insulin (EL1). The analysis of the pooled data from three studies comparing insulin and glibenclamide did not find any significant difference in the weight of the children (EL1).

The main randomised study by Langer et al. [88] (glibenclamide versus insulin) did not show any difference in the criteria for macrosomia, weight for gestational age, neonatal hypoglycaemia, admission to neonatology or foetal anomalies (EL1). The incidence of maternal hypoglycaemia was lower on glibenclamide. Insulin therapy was indicated in only 4% of patients treated with glibenclamide.

The main randomised study, The Metformin in Gestational Diabetes (MiG) trial (n = 751) (metformin versus insulin) [107], showed comparable perinatal complications in both groups (EL1) and better acceptability in the metformin group (EL1), but insulin was indicated in 46% of women on metformin. The 2009 Cochrane review [109] analysed two supplementary randomised studies (metformin versus insulin) [110, 111] and the study by Bertini et al. (glibenclamide versus insulin) [93]. The results confirmed the absence of difference in birth weight (2 studies, 93 children RR : 1.71, CI 95% (0.60-4.86)) [110, 111]. There was no significant difference in shoulder dystocia, neonatology unit admission, respiratory distress or assisted ventilation.

The risk of neonatal hypoglycaemia was increased in children born to mothers treated with insulin compared to mothers treated with OAD agents [2 studies : 114 children (RR 7.68, CI 95% (1.47-40.22)) [93, 111]. This risk was not confirmed in a very recent meta-analysis [112] (1388 patients treated with glibenclamide or metformin) [91, 111, 113, 114, 115]. Concerning maternal prognosis, the Cochrane review [109] described a significant reduction in the rates of caesarean delivery in women on OAD compared to those on insulin ; 2 studies : 90 women (RR 0.46, CI 95% [0.27-0.77]), no difference found in the last meta-analysis [112] (5 studies).

The use of OAD drugs is presently outside the scope of the MA.

The published studies concern mainly glibenclamide and metformin. Despite the absence of teratogenicity or worsening of the maternal-foetal prognosis, no study attained the statistical power needed to evaluate the risk. Furthermore, metformin crosses the placenta and no medium-term complication can be ruled out, thus requiring a long-term follow-up of children exposed in utero.

Therefore the use of OAD agents cannot be currently recommended during pregnancy.

6. Results of interventional studies

According to HAS, there is no proven benefit for treating “moderate” GDM [116]. Therefore, two questions are raised : Should patients with GDM be treated, and is there a benefit to early treatment before 24 weeks gestation ?

6.1. What are the consequences in the absence of treatment ?

One case-control study showed an increase in the number of cases of macrosomia and shoulder dystocia in patients with GDM discovered after 37 weeks gestation and left untreated. After adjustment for BMI, this difference only persisted for overweight and obese women.

Maternal BMI is a veritable risk factor in the occurrence of perinatal complications (EL3).

6.2. Specific treatment versus traditional pregnancy management

Two reviews and a meta-analysis compared specific management of GDM to traditional pregnancy management or to a “less intensive” treatment [109, 118, 119]. The studies were heterogeneous with regard to therapeutic interventions (more or less intensive dietary measures, variable self-monitoring, insulin therapy or oral antidiabetic agents). Few data were therefore pooled. Most of the selected studies had low statistical power, few were randomized and some were old.

The two main studies are recent randomised interventional studies with sufficient sample sizes : the ACHOIS and the NICHD studies, (n = 1000) [7] and (n = 958) [8], respectively.

Treatment did not result in reduced perinatal mortality. Five deaths occurred in the control group of the study by Crowther et al. [7], but the difference was not significant and the deaths were probably not related to the maternal hyperglycaemia.

The primary endpoints of the studies were composite criteria of perinatal morbidity. In the ACHOIS study [7], the composite criteria included death, shoulder dystocia, bone fractures and nerve paralysis. Their incidence was significantly reduced in the treated group (RR 0.32 ; CI 95% (0.14-0.73)) (EL1). These complications however were not significantly reduced when evaluated individually. It should be noted that the patients presenting with GDM in the control group and their doctor were unaware of the diagnosis, while it was known in the treated group. There could thus be an “under-treatment” bias in the control group and “over-treatment” in the treated group ; this might explain the greater incidence of labour induction and admissions to the neonatology unit. There was no significant difference in the NICHD study [8] for the main composite criteria integrating neonatal or perinatal deaths and neonatal complications (hyperbilirubinaemia, hypoglycaemia, hyperinsulinaemia and obstetrical trauma). The heterogeneity of the used criteria and the absence of perinatal deaths should be noted.
The reduction in the incidence of shoulder dystocia had borderline significance for Crowther et al., but was significant for Landon et al. (RR 0.37; CI 97%, 0.14-0.97, p = 0.02), as well as for the pooled data of these two studies (odds ratio 0.40, CI 95%, 0.21-0.75) [119] (EL1).

The rate of macrosomia was significantly reduced in the treated group (1030 children, RR = 0.46, CI 95%, 0.34-0.63) [7], as was the birth weight (3302 g versus 3408 g), neonatal fat mass (427 g versus 464 g), and the incidence of large-for-gestational-age infants (7.1 versus 14.5%) in the study by Landon et al. [8].

The reduction in the incidence of shoulder dystocia had borderline significance for Crowther et al., but was significant for Landon et al. (RR 0.37; CI 97%, 0.14-0.97, p = 0.02), as well as for the pooled data of these two studies (odds ratio 0.40, CI 95%, 0.21-0.75) [119] (EL1).

6.4. Potential harmful effects of treatment

No harmful effect of insulin therapy was described in the studies by Crowther et al. and Landon et al. [7, 8]. In particular, there was no report of IUGR in the treated groups, as had been suggested by Langer in cases of mean maternal glycaemia being too low [6]. The quality of life (SF-36 scale and depression score) did not appear to be altered when studied [7] (EL1).

6.5. Long-term outcomes

There are currently no data concerning the long-term outcomes of children according to the type of therapeutic intervention.

A single study on the long-term maternal outcomes is available [121]; similar results were found regardless of the therapeutic management: 35% versus 36% of patients will develop diabetes within 16 years of their delivery.

Conclusion

The ACHOIS and NICHD studies validated the importance of treating GDM (dietary, weight gain control, self-monitoring of blood glucose, insulin therapy if indicated), including cases with a low degree of severity for improving the maternal and fetal prognosis, with however a potential risk of modification of obstetrical behaviours (labour induction and transfer to neonatology unit) (EL1).

7. Conflict of interests

No conflict of interests related to the article

References


Slieker LJ, Brooke GS, Dimarchi RD. Modifications in the B10 and [65]

Hoffmann T, Horstmann G, Stammberger I. Evaluation of the repro-

Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran [61]


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