Prepregnancy BMI influences maternal and fetal outcomes in women with isolated gestational hyperglycaemia: A multicentre study

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Abstract

\textbf{Aim.} – This multicentre study analyzed the maternal and fetal outcomes of women who had one elevated 3-h oral glucose tolerance test (isolated gestational hyperglycaemia [IGH]).

\textbf{Methods.} – From 1999 to 2003, data were collected for 606 IGH women from 31 Italian obstetric or diabetic centres, including time and mode of delivery, gestational hypertension, preeclampsia, eclampsia, congenital malformations, and neonatal mortality and morbidity, to compare them with the general pregnant Italian population. A prognostic model for the outcome of pregnancy was constructed, and the concurrence of certain specified conditions was considered a positive outcome, whereas pregnancies that failed to meet one or more of the stated conditions were classified as “complicated.”

\textbf{Results.} – Macrosomia was significantly more frequent in women with IGH than in the normal pregnant population (10.7 vs 7.4\%, respectively; \(P = 0.003\)). Stillbirth and neonatal mortality rates did not differ from those in normal pregnancies, while a slight rise in the frequency of major malformations was not statistically significant (1.48 vs 0.89\%, respectively; \(P < 0.11\)). Multivariate logistic analyses confirmed that the prepregnancy body mass index (BMI) was an independent predictor of a complicated pregnancy. As for fetal growth, multivariate logistic analyses according to BMI showed that being overweight or obese were strong predictors of macrosomia.

\textbf{Conclusion.} – These findings in a large cohort of Italian women with IGH confirm the detrimental effect of even minimally altered glucose tolerance on fetal outcome. Also, prepregnancy obesity plays an important role in raising the risk of adverse perinatal outcomes in such patients.

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Keywords: Isolated gestational hyperglycaemia; Gestational diabetes; Prepregnancy overweight; Prepregnancy obesity

Résumé

L'indice de masse corporelle qui précède la grossesse influence le pronostic maternel et foetal des femmes présentant une hyperglycémie gestationnelle isolée : étude multicentrique.

\textbf{Buts.} – L’objectif de cette étude multicentrique était d’analyser les événements maternels et fetaux chez des femmes présentant un seul valeur anormale de l’hyperglycémie provoquée orale avec 100 g de glucose (hyperglycémie gestationnelle isolée).

\textbf{Patients et méthodes.} – Entre 1999 et 2003, nous avons recueilli les données de 606 femmes issues de 31 centres hospitaliers de gynécologie-obstétrique ou de diabétologie italiens, en enregistrant le terme et la voie d’accouchement, ainsi que la fréquence des hypertension artérielle, des pré-éclampsies et des toxémies gravidiques, des malformations fetales, la morbidity et mortalité néonatales, en les comparant à la population générale italienne. Un modèle pronostique a été construit sur ces éléments pour évaluer l’évolution favorable ou non de la grossesse.

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Résultats. – La survenue d’une macrosomie était significativement plus fréquente chez les femmes présentant une hyperglycémie gestationnelle isolée que dans la population témoin (10,7 vs 7,4 %; \(P = 0,003\)). Le taux de mort fœtale in utero et la mortalité néonatale n’étaient pas différents de ceux des grossesses normales. Il existait une tendance non significative en faveur d’une augmentation des malformations chez les nouveau-nés de mère atteinte d’hyperglycémie gestationnelle isolée (1,48 vs 0,89 %; \(P = 0,11\)). Analysé par régression logistique multivariée, l’indice de masse corporel maternel était un élément prédicatif indépendant de grossesse compliquée. Le surpoids et l’obésité étaient des indicateurs prédicatifs de macrosomie.

Conclusions. – Ces résultats, obtenus à partir d’une importante cohorte de femmes italiennes avec hyperglycémie gestationnelle isolée, confirment le rôle délétère de l’hyperglycémie modérée dans le développement de la macrosomie. Le surpoids antérieur à la grossesse est aussi un facteur prédicatif de complications périmatales dans cette population.

Mots clés : Hyperglycémie gestationnelle isolée ; Diabète gestationnel ; Surpoids maternel ; Obésité maternelle ; Étude longitudinale ; Macrosomie

1. Introduction

The pregnancy outcomes in women with gestational diabetes mellitus (GDM) may be complicated by perinatal morbidity and mortality, and such mothers are also at higher-than-normal risk of developing diabetes later in life [1]. This highlights the importance of early identification of GDM [2,3]. In Italy, universal screening is recommended, using a 50-g glucose challenge test (GCT) between weeks 24 and 28 of gestation [3], and plasma glucose levels greater or equal to 140 mg/dL (7.8 mmol/L) 1 h after the glucose load call for a confirmatory 3-h 100-g oral glucose tolerance test (OGTT). According to Carpenter and Coustan’s criteria [4], the diagnosis of GDM requires that two or more glucose values be met or exceeded. At present, it is common practice to consider women with only one abnormal OGTT value as non-pathological (isolated gestational hyperglycaemia [IGH]), and as having the same risk of adverse perinatal outcomes as women whose OGTT values are all in the normal range (normal glucose tolerance [NGT]). However, this remains a matter of debate, as some authors have found no difference in pregnancy outcomes between IGH and NGT [5,6], while others have reported that women with IGH had more obstetric complications, and higher rates of macrosomia and large-for-gestational age (LGA) newborns, than did women with NGT or successfully treated GDM [7–10].

In this retrospective multicentre study of Italian women, the outcome of pregnancies in women with IGH left untreated after the diagnostic test were examined to determine which clinical factor(s) influenced the perinatal results. Also, the impact of different degrees of maternal pregestational overweight status on maternal and fetal outcomes, as well as the mild glucose intolerance indicated by IGH, were analyzed.

2. Patients and methods

The present study population was drawn from patients attending 31 diabetic centres in Italy between January 1999 and December 2003, where women were routinely screened between weeks 24 and 28 of gestation. Only those women considered to be at high risk, according to the scoring system recommended by the Italian Society of Diabetology at the time the study was initiated [11], were tested before week 24; however, in this group, too, and in the absence of a diagnosis of GDM, the screening procedure was repeated at weeks 24 and 28. Screening consisted of a 50-g GCT [3,12], and the test was considered positive if the 1-h glucose was greater or equal to 140 mg/dL (≥ 7.8 mmol/L); these women were then scheduled to undergo a 100-g OGTT, which was interpreted according to Carpenter and Coustan’s criteria [4]. Women with one OGTT value greater than or equal to the cut-off value were diagnosed with IGH, while those who had at least two elevated plasma glucose values were diagnosed as GDM [2,3].

All pregnant women with IGH who delivered were recruited into the study, which was approved by the local ethics committee, whereas patients with prepregnancy diabetes were excluded. In addition, and in keeping with the current practices, the women with IGH received no treatment or specific advice during their pregnancy, but were given only conventional care. All of these women also had their demographic, anthropometric and clinical data, such as age, prepregnancy body weight, weight gain during pregnancy, family history of diabetes and obstetric history, recorded. Weight and height were measured directly, while each woman reported her own prepregnancy weight. The prepregnancy body mass index (BMI) classifications were defined as follows [13]: underweight BMI less than 18.5 kg/m 2; normal pregnancy body mass index (BMI) 18.5–25.0 kg/m 2; overweight BMI 25.1–30.0 kg/m 2; and obese BMI greater than 30.0 kg/m 2. Gestational age was estimated from the last menstrual period, which was confirmed or corrected by ultrasonography.

For maternal outcomes, all cases of gestational hypertension, preeclampsia and eclampsia, time and mode of delivery and maternal mortality were recorded; for neonatal outcomes, length and weight at birth, and any congenital malformations were noted. Shoulder dystocia, hypoglycaemia, neonatal asphyxia, hyaline membrane disease (HMD), fetal distress, obstetric trauma, hyperbilirubinaemia, stillbirths and neonatal deaths were also recorded, and contributed to the composite outcome. The absence of these factors was considered a positive outcome, while pregnancies presenting with one or more of these morbidities were classified as “complicated”.

Pregnancy-induced hypertension, preeclampsia and eclampsia were defined according to the report of the US National High Blood Pressure Education Program’s Working Group on High Blood Pressure in Pregnancy [14]. Preterm deliveries were those that occurred before week 37. Infants were considered macrosomic when their birth weight was greater or equal to 4000 g, and large for gestational age (LGA) when their size was greater than 90th percentile on the basis of gender-specific growth standards.
developed specifically for the Italian population [15]. We also calculated the ponderal index (PI) as the ratio of body weight to length cubed (g/cm³), and considered a PI greater than 2.85 as excessive [16]. Malformations were classified according to the European Surveillance of Congenital Anomalies (EUROCAT) registries [17]. Fetal morbidity was classified according to the obstetric quality indicators and data collection (OBSQID) project [18]. Stillbirths referred to those infants born dead after 180 days of pregnancy, and neonatal mortality was the rate of deaths before day 28 of life.

Maternal and perinatal outcomes were compared with the national data found in the 1999–2003 Italian perinatal database (ISTAT) [19–21]. However, such comparisons were only possible for the limited number of maternal and neonatal parameters available in the database (caesarean sections, preterm deliveries, neonatal weight, and neonatal mortality and malformations).

Maternal HbA1c levels were measured using standard high-performance liquid chromatography (HPLC) [22], and the normal range was 4.0–5.5% (95% confidence interval [CI]: 2.5–97.5%) [23].

2.1. Statistical analysis

Data are presented as means ± standard deviations (SD) for continuous variables and as proportions for categorical variables. Groups were compared for either categorical data or frequency of an event using the χ² test with Yates’ correction and Fisher’s test whereas, for continuous variables, the Mann–Whitney non-parametric U test was used.

Event frequency in both the study sample and general population, based on the 1999–2003 ISTAT [19–21], was compared using a one-sample proportion test with continuity correction. All tests were two-sided and P < 0.05 was considered significant.

A prognostic model of pregnancy outcome was constructed, and the concomitance of several conditions (delivery after week 37, no hypertension, no preeclampsia, no caesarean sections, birth weight less than 4 kg, adequate growth for gestational age, PI less than 2.85, no malformations and no fetal mortality) was considered a positive outcome. Pregnancies that did not meet one or more of the above criteria were classified as “complicated”.

Univariate and multiple logistic-regression analyses were used to explore the crude and adjusted effects of clinical and anthropometric characteristics in complicated pregnancies. Statistical analyses were carried out using the SPSS 13 for Windows and open-source R software.

3. Results

Each centre supplied data for every diabetic pregnancy during the study. In all, the 31 centres collected data on 606 IGH patients, for whom the main clinical characteristics and outcomes are summarized in Table 1.

On the basis of the prepregnancy BMI, 3.3% of women were classified as underweight, 57.6% as normal weight, 24.4% as overweight and 14.7% as obese. Morbid obesity (BMI greater than 35 kg/m²) was found in 10.6% of cases, and extreme obesity (BMI greater than 40 kg/m²) in 6.6%. HbA1c at the time of diagnosis was within the normal range. The caesarean-section rate was no different from that in the normal pregnant population (34.3 vs 33.2%, respectively; P = 0.5), and the rate of preterm deliveries was only slightly higher (6.6 vs 5.8%, respectively) and not significant (NS). Patients who developed preeclampsia were diagnosed with IGH earlier (before week 24) than those who did not (P = 0.007).

Concerning the main fetal outcomes (Table 2), taking the IGH group as a whole, macrosomia was significantly more frequent than in the normal pregnant population (10.7 vs 7.4%, respectively; P = 0.003); 17.7% of GDM babies were LGA, and one-third had a PI greater than 2.85. However, no differences were found in macrosomia and LGA rates between the male and female newborns, and the stillbirth and neonatal mortality rates did not differ from those of normal pregnancies (0.33 vs 0.30%, and 0 vs 0.32%, respectively; both NS). The total frequency of malformations was slightly higher among IGH babies, but the difference was not significant (1.48 vs 0.89%, respectively; P < 0.11).

In 346 women (57.1%), the pregnancy was classified as complicated. Univariate logistic-regression analyses showed that the prepregnancy BMI, both as a continuous variable and expressed as a category, was predictive of a complicated pregnancy. Multivariate logistic analyses confirmed that the prepregnancy BMI was indeed an independent predictor of a complicated pregnancy (Table 3). Also, the women with malformed infants were older and had a higher BMI score than did the mothers of infants with...

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and metabolic parameters, and maternal outcomes, in 606 women with isolated gestational hyperglycaemia (IGH).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.7 (4.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.9 (4.9)</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>11.2 (5.4)</td>
</tr>
<tr>
<td>HbA1c at time of diagnosis (%)</td>
<td>4.8 (0.9)</td>
</tr>
<tr>
<td>Gestational week at diagnosis</td>
<td>28.2 (4.8)</td>
</tr>
<tr>
<td>Caesarean section (%)</td>
<td>34.3</td>
</tr>
<tr>
<td>Preterm delivery (%)</td>
<td>6.7</td>
</tr>
<tr>
<td>Gestational hypertension (%)</td>
<td>6.1</td>
</tr>
<tr>
<td>Preeclampsia (%)</td>
<td>2.0</td>
</tr>
<tr>
<td>Eclampsia (%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) or percentage.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Fetal outcomes for 606 women with isolated gestational hyperglycaemia (IGH).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrosomia (%)</td>
<td>10.7</td>
</tr>
<tr>
<td>Large-for-gestational-age (LGA) newborns (%)</td>
<td>17.7</td>
</tr>
<tr>
<td>Ponderal index (PI) &gt; 2.85 (%)</td>
<td>34.3</td>
</tr>
<tr>
<td>Stillbirths (%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Neonatal mortality (%)</td>
<td>0</td>
</tr>
<tr>
<td>Congenital malformations (n–%)</td>
<td>9–1.48</td>
</tr>
<tr>
<td>Cardiovascular (n)</td>
<td>2</td>
</tr>
<tr>
<td>Neural-tube disease (n)</td>
<td>1</td>
</tr>
<tr>
<td>Genitourinary (n)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal (n)</td>
<td>0</td>
</tr>
<tr>
<td>Skeletal (n)</td>
<td>2</td>
</tr>
<tr>
<td>Other (n)</td>
<td>4</td>
</tr>
</tbody>
</table>

n: number.
Table 3
Predictive factors of ‘complicated pregnancy’ in women with isolated gestational hyperglycaemia (IGH).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analyses</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.991 (0.95–1.03)</td>
<td>0.6</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>1.104 (1.06–1.15)</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI classification&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>1.318 (0.53–3.25)</td>
<td>0.5</td>
</tr>
<tr>
<td>Overweight</td>
<td>2.049 (1.37–3.06)</td>
<td>0.000</td>
</tr>
<tr>
<td>Obese</td>
<td>3.97 (2.29–6.87)</td>
<td>0.000</td>
</tr>
<tr>
<td>HbA1c at time of diagnosis</td>
<td>1.025 (0.71–1.48)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Normal weight as reference (OR = 1).

Table 4
Predictive factors for macrosomia in women with isolated gestational hyperglycaemia (IGH).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.051 (0.969–1.140)</td>
</tr>
<tr>
<td>Body mass index classification&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.408 (0.152–13.067)</td>
</tr>
<tr>
<td>Underweight</td>
<td>2.715 (1.507–6.720)</td>
</tr>
<tr>
<td>Overweight</td>
<td>4.657 (1.689–12.842)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.043 (0.976–1.115)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Normal weight as reference (OR = 1).

Discussion

The present study was part of the World Health Organization (WHO) Diabetes in Pregnancy Aggregated Data European Pilot Project—Subproject Diabetes and Pregnancy, which was designed to improve the outcome and quality of care in pregnancy by collecting and analyzing data from different countries. The multicentre survey comprised a large sample population of Italian women. In addition, given that the 31 centres involved were located in northern, central and southern Italy, and that the diagnostic and metabolic surveillance methodologies were the same at all centres—and based on national guidelines—it is safe to assume that the survey offers a representative picture of pregnancy complications due to glucose intolerance in Italy.

The survey focused on women who failed to meet the current diagnostic criteria for GDM, but who had a positive 50-g GCT, which was then confirmed by one abnormal 100-g OGTT result. Several studies have suggested that even such a minimal degree of glucose intolerance in pregnancy may be associated with unfavourable fetal–maternal outcomes, with significant increases in the rates of LGA and macrosomic infants. Most studies [24–26] refer to diagnostic categories based on the old National Diabetes Data Group (NDDG) [27] or WHO [28] criteria, which were less restrictive than those originally proposed by Carpenter and Coustan, which have now been adopted internationally [4]. This means that many conditions formerly considered “minor alterations” may now be re-classified as mild forms of GDM by the newer diagnostic criteria. However, even recent studies that refer to lower degrees of hyperglycaemia, according to the new diagnostic thresholds, have—with few exceptions [29]—reported abnormal rates of adverse perinatal outcomes in women who have just one high OGTT value [30,31]. This is not surprising, as the condition involves pathophysiological alterations that are qualitatively indistinguishable from those of overt GDM, with similar patterns of insulin sensitivity and insulin secretion [32]. The present population-based survey confirms such results in a substantial series of pregnant women. Thus far, no other study has examined the natural history of pregnancy in such a large number of cases complicated by this form of mild gestational hyperglycaemia. In interpreting the present findings, however, some limitations need to be borne in mind. First, comparisons with pregnancy outcomes in the general Italian population were only possible for the limited number of factors reported in the ISTAT national database and, as neither gestational age at birth nor neonatal length are included, the rates of LGA newborns and high neonatal PI found in the present pregnancies could not be compared with those in the general population. Also, the present figures recorded appear to be high compared with those usually reported for non-diabetic pregnancies. Furthermore, in the original forms sent out to the participating study centres, only the final diagnosis was required, with no request for details of glucose times for the 100-g OGTT. As a consequence, it is not possible to establish a posteriori the precise point in the OGTT and the specific threshold of glycaemia that were related to the abnormal pregnancy outcomes. Other authors have recently found that an abnormal 1-h plasma glucose concentration was the best predictor in terms of pathophysiological involvement and clinical outcome [33,34]. Nevertheless, and despite these limitations, there was a significantly higher rate of macrosomia in the newborns of IGH out such malformations (31.0 ± 4.4 years vs 28.9 ± 4.7 years, P = 0.038, and 28.6 ± 5.2 kg/m² vs 24.8 ± 4.9 kg/m², P = 0.015, respectively).

As regards fetal growth, multivariate logistic analyses according to BMI showed that being either overweight or obese was strongly predictive of macrosomia (Table 4), whereas only being overweight was predictive of a PI greater than 2.85 (OR: 2.275; 95% CI: 1.222–4.236; P = 0.009). Furthermore, only obesity was a strong predictor of LGA (OR: 3.309; 95% CI: 1.477–7.412; P = 0.004).

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pregnancies in the present study, but no gender-related effects of maternal glucose tolerance (for example, higher rates of abnormal growth patterns in male newborns), such as were recently reported by Ricart et al. [35]. However, rates of cesarean section, stillbirths and neonatal mortality were similar to those in normal pregnancies, and the minimal rise in the frequency of major malformations was not statistically significant and, therefore, can be considered negligible.

In accordance with the recent evidence from the ACHOIS trial [36], the HAPO study [37] and the recently published randomized controlled trial by Landon et al. [38] on mild GDM, our findings suggest that, in terms of glycometabolic homeostasis in pregnancy, a clear-cut boundary between normality and GDM is no longer feasible. Indeed, it appears that even the slightest alteration in glucose tolerance can result in excessive or otherwise perturbed fetal growth, as seen in the pregnancies of women with frankly pathological metabolic disturbances.

In addition to establishing the detrimental role of even mild maternal hyperglycaemia, another important finding from our series of patients is the impact of maternal prepregnancy BMI on neonatal outcome: both the univariate and multivariate logistic analyses found that prepregnancy obesity was a strong predictor of complicated pregnancy in women with IGH. In fact, the prepregnancy maternal weight is apparently even more important than the degree of glucose abnormality, as reflected by HbA1c concentrations, which is not surprising considering the low sensitivity of such a medium-term integrated glycaemic index as is the HbA1c in pregnancy, and the extremely narrow range of glucose derangement expected in the IGH nosographical category, which lies halfway between normality and overt GDM.

Others have reported results similar to ours. In a large Spanish population in 2005, Ricart et al. [39] found that the mother’s prepregnancy BMI exerted a considerably greater influence on macrosomia and LGA than did gestational hyperglycaemia; similar results were also found by Segal et al. [40] for pregnant women with a positive 50-g GCT, but not overt GDM. The importance of the relationship between prepregnancy BMI and neonatal outcome, and its implications for the obstetric and metabolic care of women planning a pregnancy, is evident in the light of the increasing prevalence of overweight and obesity in the general population and, therefore, in women of childbearing age as well.

In conclusion, the present study involving a large cohort of Italian women with only one abnormal OGTT value confirms the previous reports of the potentially detrimental effects of even minimally altered glucose tolerance in pregnancy. In addition, the clearly predictive role of maternal BMI on adverse pregnancy outcomes, despite a non-overt diabetic state, highlights the need for pregnancy-prevention programmes and counselling for obese women of childbearing age to encourage them to lose sufficient weight before conceiving.

**Conflict of interest**

No potential conflict of interest relevant to this article is reported.

**Appendix A.**

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**References**


[33] Ratnakaran R. Impaired glucose tolerance in pregnancy is a heterogeneous metabolic disorder as defined by the glycaemic response to the oral glucose tolerance test. Diabetes Care 2006;29:57–62.


