Med Clin (Barc). 2015;145(6):269–272

MEDICINA CLINICA

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Current treatment for gestational diabetes☆

Tratamiento actual de la diabetes gestacional

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ARTICLE INFO

Article history:
Received 9 March 2015
Accepted 23 April 2015
Available online 4 March 2016

Question

What should be the treatment of choice in gestational diabetes (GD)?

Reply

GD is a metabolic disorder that is diagnosed by first-time documentation of hyperglycaemia (whether baseline or in an oral glucose challenge test) during pregnancy.[1] It has been estimated that it could be observed in 12% of pregnancies worldwide, although its prevalence and diagnosis in different countries is very variable (figures range between <1% and 28%).[2] In Europe, a prevalence of 2–6% was observed in a narrative review of the publications produced from 2000 to 2009.[3] In a Spanish study published in 2003, it was 4.67%, a figure in line with that of other previous studies, also performed in an autochthonous Spanish population (2–5%).[4] In addition, it should be noted that GD diagnosis has progressively increased in recent years. In a study conducted in the United States,[5] for example, between 1993 and 2009, the age-adjusted prevalence was observed to grow from 3.09 to 5.57 cases/100 births ($p < 0.001$). Potential explanations for this include a change in the diagnostic criteria for GD that were proposed based on the results of the HAPO study.[6] In a retrospective study, for example, it was observed that, had these criteria been applied to a historic cohort, the prevalence of GD would have gone from 4.6% to 12.4%.[7] In any case, given that these criteria started to come into widespread use in 2010, this evolution may also be due to other factors (for example, increased maternal age and prevalence of obesity).[8]

Currently, in developed countries, diagnosis tends to be done by means of systematic screening of pregnant women. Therefore, its significance derives from not so much its clinical manifestations (the majority of women are asymptomatic) as its potential complications. Notable maternal complications include pre-eclampsia and Caesarean birth, and notable foetal complications include large-for-gestational-age (LGA) newborns, macrosomia, shoulder dystocia, neonatal hypoglycaemia and perinatal mortality.[9–11] In addition, GD has been associated with a slightly but significantly increased (relative risk [RR] of 1.16; 95% confidence interval [CI] of 1.07–1.25, in cohort studies and an odds ratio [OR] of 1.4; 1.22–1.62) in case and control studies incidence of major malformations, which contrasts with the greater magnitude of this association observed in women with pre-gestational diabetes (RR = 2.66; 95% CI 2.04–3.47; and OR = 4.7; 3.01–6.95).[12] A meta-analysis of the randomised studies published up to 2009 that evaluated the effect of specific treatment (diet with or without insulin) and the intensity of this effect on these outcomes[13] concluded that this only significantly decreased some perinatal complications, such as the incidence of LGA newborns and shoulder dystocia. Another meta-analysis that included clinical trials and cohort studies published up to 2012 and evaluated the same outcomes[14] concluded that GD treatment significantly decreased the incidence of pre-eclampsia, shoulder dystocia and macrosomia (birth weight >4000 g).

A consensus document by the Spanish Diabetes and Pregnancy Group (GEDE) published in 2006[1] specified that the management of GD should start with dietary measures and exercise; this does not differ substantially from recommendations by other authors and recommendations intended for non-pregnant diabetic patients.[15,16] Starting drug treatment is recommended if appropriate metabolic control is not achieved or if ultrasound monitoring confirms foetal macrosomia. Although this document specifies that

☆ Please cite this article as: Salat D, Aguilera C. Tratamiento actual de la diabetes gestacional. Med Clin (Barc). 2015;145:269–272.

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the treatment of choice is insulin, references to the possibility of using oral hypoglycaemic agents (OHAs) are already being collected.

The first randomised study in which treatment with insulin was compared to treatment with glibenclamide was published in 2000.[17] A total of 404 women with GD who required drug treatment were enrolled. They were randomised to receive insulin (starting dose 0.7 mg/kg/day, adjusted according to response) or glibenclamide (starting dose 2.5 mg/day, adjusted up to a maximum of 20 mg/day according to response) starting between weeks 11 and 33 of pregnancy. Although appropriate metabolic control was not achieved in 8 of the patients treated with glibenclamide and they were switched to insulin, no differences were observed in the primary endpoint: mean plasma blood glucose, which was 114 ± 19 mg/dl in the group treated with glibenclamide and 116 ± 22 mg/dl ($p = 0.33$) in the group treated with insulin. Differences in the incidence of adverse foetal events were also not reported (glibenclamide and insulin groups, respectively): LGA newborns (24 and 26; $p = 0.76$), macrosomia (14 and 9; $p = 0.26$), neonatal hypoglycaemia (12 and 18; $p = 0.25$), congenital malformations (4 and 5; $p = 0.74$) and intrauterine death (one in each group; $p = 0.99$).

In a subsequent study, Silva et al.[18] randomised 36 women to adhere to treatment with insulin and 32 women to take glibenclamide. Six of the patients treated with glibenclamide required treatment with insulin. No differences were observed in the mean blood glucose of the participants in each group. Mean newborn weight was greater in the group that took glibenclamide (3372 ± 501 g versus 3083 ± 423 g; $p = 0.01$), as was the proportion of macrosomia (15.62% versus 0%; $p = 0.02$) and that of neonatal hypoglycaemia (<40 mg/dl) (25% versus 2.78%; $p = 0.01$).

In a meta-analysis[19] of 5 randomised clinical trials (674 patients included), in comparison with insulin, treatment with glibenclamide was associated with a greater risk of post-natal hypoglycaemia (RR = 1.98; 1.17–3.36) and macrosomia (2.22; 1.07–4.61). Estimated mean differences also showed greater birth weight (0.21; 0.06–0.36). No differences were observed in any of the other variables evaluated (blood glucose management, Caesarean or pre-term birth, LGA newborns, neonatal hypocalcaemia and congenital malformations).

Rowan et al.[20] conducted a clinical trial in which they enrolled 751 patients, who were randomised to receive treatment with insulin or metformin. No differences were observed in the primary endpoint of the trial (comprising neonatal hypoglycaemia [<28.8 mg/dl], respiratory distress, need for phototherapy, birth trauma, score <7 after 5 min on the Apgar scale and prematurity [birth before 37 weeks]): 32.2% in the group that received insulin and 32% in the group that received metformin (RR = 0.99; 95% CI 0.8–1.23). The components of this endpoint were analysed separately, and significant differences were only observed for neonatal hypoglycaemia (8.1% in the insulin group versus 3.3% in the metformin group; $p = 0.008$) and prematurity (12.1% in the metformin group versus 7.6% in the insulin group; $p = 0.04$). Among women who took metformin, 46.3% required addition of insulin to optimise blood glucose management, but this was not associated with significant differences in the results of the primary endpoint (34.5% versus 29.7% of those who did not require additional treatment; $p = 0.33$). Women treated with metformin had less weight gain in weeks 36 and 37 of pregnancy (0.4 ± 2.9 kg versus 2 ± 3.3 kg; $p < 0.001$). The proportion of women who were shown to be predisposed to take the medicine that they had received again in future pregnancies was greater in the group randomised to metformin (76.6% versus 27.2%; $p < 0.001$). There were no differences in other variables, nor in adverse effects, including congenital malformations.

A meta-analysis[21] of 5 randomised clinical trials (1270 patients included) also concluded that metformin is comparable to insulin in maternal blood glucose management and neonatal outcome, while another that included 1420 patients (participants in 6 trials)[22] found statistically significant differences in 3 variables—lower weight gain during pregnancy (mean of 9.54 kg versus 10.8 kg), higher rate of premature births (10% versus 6.4%) and lower prevalence of neonatal hypoglycaemia (12.8% versus 16.6%)—among women who were treated with metformin.

These 2 OHAs have also been compared to each other. A study by Silva et al.[23] found that women treated with metformin (n = 32) had lower weight gain during pregnancy than those treated with glibenclamide (n = 40): 10.3 ± 5.8 kg versus 7.6 ± 8.1 kg; $p = 0.02$. Although differences were not statistically significant, a lower proportion of children of women treated with metformin had macrosomia (6.2% versus 15%) or was LGA newborns (9.4% versus 22.5%). There were no differences in all other variables analysed, including degree of glucose management achieved with each treatment.

By contrast, a study by Moore et al.[24] found a greater rate of failures in blood glucose management in women treated with metformin (n = 75) than in those treated with glibenclamide (n = 74) (OR = 2.7; 1.2–3.9).

The most recent meta-analyses of comparative clinical trials between insulin and OHAs performed in women with GD have shown that metformin (together with on-demand administration of insulin to optimise blood glucose management) is superior to insulin alone, and both are superior to glibenclamide.[25,26] It should be noted that one of them[21] evaluated the quality of the original trials and found that some had significant methodological limitations, such as the absence of a written protocol or a high drop-out rate, and that sometimes there were discrepancies between what was presented in the "methods" and "results" sections. In addition, the authors noted that all trials were open-label.

Regarding the foetal safety of OHAs, studies in animals have not shown either metformin or glibenclamide to have a teratogenic effect. The evidence in favour of its safety during pregnancy in humans transcends that deriving from the above-mentioned clinical trials. However, it should be noted that, in the majority, the start of treatment with OHAs was after the first trimester, when the period of organogenesis had already been completed. However, there are data on exposure to metformin in the first trimester of pregnancy in women who were taking the drug for polycystic ovary syndrome and/or pre-gestational diabetes. No increased risk of foetal malformations has been observed in these women.[27] Although limited and short-term (18 months of age in follow-up), some data have shown that prenatal exposure to metformin does not adversely affect postnatal motor, linguistic or social development.[28]

The data for acarbose are very limited,[29,30] and the use of other agents in this indication has not been formally evaluated.

Despite not being referred to in the summary of product characteristics, the advantages in terms of cost and convenience that OHAs represent compared to insulin have promoted their use in the treatment of GD. In this regard, a North American study that retrospectively evaluated the use of glibenclamide and insulin in GD from 2000 to 2011[31] showed that there the use of glibenclamide had progressively increased: in 2007, it became the most used drug, and by the end of the study period, 64.5% of women who required drug treatment for GD were treated with glibenclamide. At present, scientific associations have not unanimously positioned themselves in relation to their use. On the one hand, the American College of Obstetrics and Gynecology includes in a clinical practice guideline[32] the statement that, if necessary, treatment with insulin and treatment with OHAs (it only mentions glibenclamide