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CLINICAL ARTICLE

Twin pregnancy among women with pregestational type 1 or type 2 diabetes mellitus

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ABSTRACT

Objective: To assess the impact of twin versus singleton pregnancy on obstetric and perinatal outcomes among women with pregestational diabetes mellitus (DM). *Methods:* Multicenter retrospective cohort study of women with pregestational DM and twin or singleton pregnancy, conducted in Spain during 2005–2010. Each group included 63 women (type 1 DM, n = 39; type 2 DM, n = 24). *Results:* Of 269 565 deliveries, 68 (0.025%) were twins of mothers with pregestational DM, with 28/63 (44.4%) conceptions achieved with assisted reproduction technology. Among women with type 1 DM, hypertensive complications were more common among those with twins than among controls (13% versus 3%, $P = 0.02$); the rate of preterm birth was higher (69% versus 15%, $P < 0.001$); and the rate of admission to the neonatal intensive care unit was higher (51% versus 21%, $P = 0.005$). Twin pregnancy was an independent risk factor for adverse perinatal outcomes regardless of the type of diabetes. *Conclusion:* Twin pregnancy in women with either type of DM dramatically increased the risk of perinatal morbidity. In mothers with type 1 DM, twin pregnancy was more often associated with hypertensive complications than singleton pregnancy. Transfer of more than one embryo should be avoided if ART is needed in a woman with DM.

1. Introduction

The rate of twin births increased by 50%–76% between 1980 and 2009 in high-resource countries, mainly because of the expanded use of assisted reproduction technology (ART) [1]. Currently, twin pregnancies account for 3% of all pregnancies in the USA [2] and 2% in Spain [3].

The prevalence of pregestational diabetes mellitus (DM) has also significantly increased, from 3.1 per 1000 births in 1998 to 4.7 per 1000 births in 2004 in the north of England [4], mainly because of an increase in obesity-associated type 2 DM [5].

Pregestational DM and twin pregnancy are both risk factors for complications, but the effect of their simultaneous occurrence on obstetric and perinatal outcomes has not yet been established [6], probably because this combination is so rare. In a previous study [7], twin pregnancy in women with gestational diabetes was associated with a higher risk of hypertensive complications, prematurity, and macrosomia, whereas the risk of the infant being small for gestational age was significantly reduced. Pregestational DM is a far more serious pathology than gestational diabetes. The aim of the present study was therefore to assess the impact of twin versus singleton pregnancy on obstetric and perinatal outcomes among women with pregestational DM, with separate analyses being conducted for type 1 and type 2 DM.

2. Materials and methods

The present multicenter retrospective cohort study was performed by the Spanish Diabetes and Pregnancy Study Group at nine tertiary university hospitals in Spain. Medical records were reviewed to identify women with pregestational DM (type 1 or type 2) who gave birth to

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twins between January 1, 2005, and December 31, 2010. Diabetes was defined according to the classification of the American Association of Diabetes [8]. For each eligible woman with a twin pregnancy, the next consecutive woman with pregestational DM of the same type and a singleton pregnancy was included in a control group. The study was approved by the institutional review board at the University Hospital of the Canary Islands. Informed consent was not needed because of the retrospective nature of the study.

The inclusion criteria were a pregnancy duration of 22 weeks or more and a birthweight of 500 g or more. The absence of reliable data in the clinical history was a criterion for exclusion.

During the 6-year study period, 269 565 pregnancies were recorded, 8626 (3.2%) of which were twin pregnancies. Pregestational DM was present in 68 mothers. Therefore, the two complications coexisted in 2.5 of 10 000 pregnancies, and the mother had pregestational DM in 7.9 of 1000 twin pregnancies.

Five pregnancies (type 1 DM, n = 3; type 2 DM, n = 2) were excluded because of incomplete data. The final analysis included 63 women with pregestational DM and a twin pregnancy and 63 controls with pregestational DM and a singleton pregnancy. To assess the effect of the type of DM, four subgroups were established. Subgroup 1 comprised women with a twin pregnancy and type 1 DM (n = 39), subgroup 2 comprised women with a twin pregnancy and type 2 DM (n = 24), subgroup 3 comprised women with a singleton pregnancy and type 1 DM (n = 39), and subgroup 4 comprised women with a singleton pregnancy and type 2 DM (n = 24).

Similar numbers of twin and singleton pregnancies were included from each center. The diabetes management protocol was based on the recommendations of the Spanish Diabetes and Pregnancy Study Group [2] and was the same at all hospitals.

Data on maternal demographics and history of chronic hypertension were collected from the clinical records. The use of ART, including artificial insemination, in-vitro fertilization (IVF), intracytoplasmic sperm injection, and oocyte donation, was also recorded. The pregnancy duration (completed weeks of pregnancy) was determined based on the insemination or embryo transfer date or, in spontaneous pregnancies, on the first-trimester ultrasound findings.

In addition, data on the duration, complications, and treatment of diabetes were collected. Glycosylated hemoglobin (HbA1c) levels in each trimester of pregnancy were recorded and expressed as standard deviation from the mean for the relevant reference laboratory. Treatment guidelines for DM were similar in all participating hospitals [9].

Hypertensive complications of pregnancy were diagnosed and their severity was graded in accordance with the criteria of the International Society for the Study of Hypertension in Pregnancy [10]. Chorionicity was assessed by ultrasound and confirmed after delivery.

The following obstetric and perinatal outcomes were analyzed: gestational age at delivery, prematurity (pregnancy duration <37 or <34 weeks), mode of delivery (vaginal or cesarean), and birthweight. The birthweight was converted into a percentile after correction for sex and gestational age at delivery using Spanish standards for twin and singleton pregnancies [11,12], and the infants were classified as large for gestational age (LGA) or small for gestational age if the birthweight was above or below the customized cut-off for the 90th or 10th percentile, respectively. Apgar scores at 1 and 5 minutes, umbilical artery pH level, neonatal hypoglycemia (<40 mg/dL in the first 24 hours of life), admission to the neonatal intensive care unit (NICU), presence of major congenital malformations (those causing death, significant disabilities, or requiring major surgery for correction), and perinatal mortality were also assessed. A stillbirth or fetal mortality was defined as death in utero of one or both fetuses (weight >500 g or pregnancy duration >22 weeks). Early neonatal mortality was defined as death of a live-born infant before the 7th day of life. The perinatal mortality figures included both fetal and early neonatal deaths.

The distribution of variables was assessed using the Kolmogorov–Smirnov test. Differences between the groups were analyzed using the t test. For the comparison of qualitative variables, the χ^2 test or the Fisher exact test were used (the Fisher exact test was used if a value was expected to be lower than 5). Logistic regression was used to assess the influence of twin pregnancy on perinatal outcomes, with maternal characteristics (age, body mass index [BMI], and parity) and the severity of diabetes as covariates. Severe diabetes was defined by the presence of at least one of the following complications: retinopathy, nephropathy, chronic hypertension, and peripheral neuropathy.

Multiple stepwise linear regression was used to predict the birthweight and the birthweight percentile, using BMI, pregnancy duration, and maternal age as covariates, and sex of the infant, twin pregnancy, nulliparity, and severity of diabetes as predictive factors. The relationship between prematurity and NICU admission was also evaluated. Finally, the effect of the interaction between the type of diabetes and twin pregnancy was included in the model.

Statistical analyses were performed with SPSS version 19.0 (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

3. Results

Women with diabetes who had a twin pregnancy were older than those with a singleton pregnancy (33.6 ± 4.8 years versus 31.9 ± 5.2 years), but the difference was not statistically significant ($P = 0.06$). However, among women with type 1 DM, those with a twin pregnancy were significantly older than those with a singleton pregnancy ($P < 0.01$) (Table 1). The pregestational BMI and the rates of obesity and nulliparity were similar in the 2 groups.

Overall, 28/63 (44.4%) twin pregnancies and 7/63 (11.1%) singleton pregnancies were achieved with ART (Table 2). ART was more common in twin pregnancies, both in the group with type 1 DM and in the group with type 2 DM ($P < 0.001$ and $P = 0.05$, respectively).

The duration of diabetes was 12.2 ± 7.7 years and 10.5 ± 7.4 years in the twin and singleton pregnancy groups, respectively ($P = 0.2$). All pregnant women were treated with fast-acting and intermediate-acting insulin, except for nine (7.1%) women who received glargine (twin pregnancy, n = 6 [4.8%]; singleton pregnancy, n = 3 [2.4%]). The frequency of treatment with continuous subcutaneous insulin infusion (CSII) was similar among women with twin and singleton pregnancies (n = 12 [19.0%] versus n = 11 [17.5%]) (Table 3).

The standard deviations of the HbA1c levels were similar for the two groups throughout pregnancy: first trimester, 1.4 ± 1.0 versus 1.6 ± 0.9 ($P = 0.03$); second trimester, 0.9 ± 0.9 versus 1.2 ± 0.9 ($P = 0.1$); and third trimester, 1.1 ± 0.8 versus 1.1 ± 0.8 ($P = 0.9$). Table 3 shows the corresponding values by type of DM.

Worsening of pregestational retinopathy was seen in 3 (50.0%) women with type 1 DM and a twin pregnancy, whereas no progression was observed in those with a singleton pregnancy and in women with type 2 DM. The data coding system did not allow assessment of the evolution of pre-existing, or the onset of new, diabetic nephropathy during pregnancy.

All twin pregnancies were dichorionic with the exception of two (5.1%) monochorionic diamniotic pregnancies in the type 1 DM group and another two (8.3%) in the type 2 DM group.

One (2.6%) twin pregnancy in a woman with type 1 DM was complicated by the twin-to-twin transfusion syndrome. It was successfully treated with laser coagulation.

The rate of hypertensive complications among women with pregestational DM was higher in the twin pregnancy group (n = 8 [12.7%]) than in the singleton pregnancy group (n = 2 [3.2%]), but the difference was not significant ($P = 0.08$). However, if only the women with type 1 DM were considered, those with a twin pregnancy had significantly more hypertensive complications than those with a singleton pregnancy ($P = 0.02$) (Table 4).

The gestational age at delivery was significantly lower in the twin pregnancy group than in the singleton pregnancy group (34.8 ± 3.3 weeks versus 37.8 ± 1.5 weeks, $P < 0.001$). The rate of preterm

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