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Risk of gestational diabetes mellitus in patients undergoing assisted reproductive techniques

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ABSTRACT

Objective: To compare the incidence of gestational diabetes mellitus (GDM) between pregnancies conceived spontaneously and pregnancies conceived following assisted reproductive technology (ART).
Study design: This cross-sectional study evaluated the medical records of 215 women who conceived spontaneously and 145 women who conceived following ART from September 2011 to October 2012. Exclusion criteria were: polycystic ovary syndrome, maternal age ≥40 years, family history of diabetes in first-degree relatives, pre-pregnancy diabetes, glucose intolerance treated with hypoglycaemic agent (e.g. metformin), history of GDM, history of stillbirth, recurrent miscarriage, history of baby with birth weight ≥4 kg (macrosomia), parity >3, Cushing syndrome, congenital adrenal hyperplasia and hypothyroidism. For better comparison of the incidence of GDM, the ART group was further subdivided into: (i) an in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) group (n = 95); and (ii) an intrauterine insemination (IUI) group (n = 50). The diagnosis of GDM was based on the criteria of the American Diabetes Association.
Results: The incidence of GDM was significantly higher in the IVF/ICSI and IUI groups (43% and 26%, respectively) compared with the spontaneous pregnancy group (10%). Age, pre-pregnancy body mass index (BMI) and weight gain in pregnancy were similar among women with GDM in all three groups. In addition, the incidence of pregnancy-induced hypertension was significantly higher in the IVF/ICSI group (21%) compared with the spontaneous pregnancy group (7%). Logistic regression analysis demonstrated four strong risk factors for GDM: age, BMI, mode of ART and progesterone use during pregnancy.
Conclusion: This study indicated that the risk of GDM is two-fold higher in women with singleton pregnancies conceived following ART compared with women who conceived spontaneously. In addition, progesterone use during pregnancy was found to be an important risk factor for GDM. This subject requires further study.

Introduction

Gestational diabetes mellitus (GDM) is a common endocrine disorder in pregnancy [1], where women without a previous diagnosis of diabetes exhibit high blood glucose levels and carbohydrate intolerance, especially during the third trimester [1]. The reported prevalence of GDM ranges between 1% and 14% of all pregnancies, depending on the population studied and the diagnostic tests used [1]. However, the incidence of diabetes during pregnancy has increased in recent years to approximately 40% [2]. GDM is associated with increased risk of maternal, fetal and neonatal complications, such as pre-eclampsia, caesarean delivery, macrosomia, shoulder dystocia, birth injuries, respiratory distress syndrome, hypoglycemia and jaundice [1,2]. Up to one-half of women with GDM will develop type 2 diabetes later in life [1,2].

It is important to understand the risk factors of GDM in order to provide timely diagnosis and appropriate care. The most important risk factors are: family history of diabetes, advanced maternal age, obesity, high parity, previous adverse pregnancy, non-white race,

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history of baby with birth weight >3800 g and hypothyroidism [1,3]. Recent studies have shown that in addition to the above risk factors, singleton and twin pregnancies resulting from assisted reproductive techniques (ART) have been associated with increased risk of GDM [4–9]. In addition, risk factors for GDM, such as age, multiple pregnancy, obesity and polycystic ovary syndrome (PCOS), are often seen among women undergoing in-vitro fertilization (IVF) [10]. The increasing number of pregnancies resulting from ART and increased awareness of GDM-related morbidity has led to research on possible differences in pregnancy outcomes between ART and non-ART pregnancies with GDM [10]. A recent study by Marchand et al. [11] found that the rate of GDM was lower among women who conceived following intracytoplasmic sperm injection (ICSI) compared with women who conceived spontaneously, following IVF or following simple ART. The higher rate of GDM in these patients, independent of age and parity, may be due to: (i) etiology of infertility; (ii) types of drugs used for ovulation induction and luteal phase support; (iii) changes in the hormonal environment due to increased hormone levels after ovulation induction and during early pregnancy; and (iv) presence of underlying metabolic and vascular factors exacerbated during ovulation induction and IVF/ICSI procedures [4–6]. To increase knowledge in this field, this cross-sectional study was designed to compare the incidence of GDM in pregnancies conceived spontaneously and pregnancies conceived following ART.

Materials and methods

This cross-sectional study was performed at the Reproductive Biomedicine Research Centre of the Royan Institute, Tehran, Iran between September 2011 and October 2012. The ART group consisted of women with singleton pregnancies conceived following fresh IVF/ICSI or intrauterine insemination (IUI) at the Royan Institute. The control group consisted of women with singleton spontaneous pregnancies who were referred to Akbarabadi Women's Hospital, affiliated with Tehran University of Medical Science, over the same period of time. The exclusion criteria were: polycystic ovary syndrome, maternal age ≥40 years, family history of diabetes in first-degree relatives, pre-pregnancy diabetes, glucose intolerance treated with hypoglycemic agent (e.g. metformin), history of GDM, history of stillbirth, recurrent miscarriage, history of baby with birth weight ≥4 kg (macrosomia), parity >3, Cushing syndrome, congenital adrenal hyperplasia and hypothyroidism.

Fasting plasma glucose was measured in the first trimester for all participants. In accordance with the criteria of the American Diabetes Association (2005), pregnant women were screened at 24–28 weeks of gestation using a 50-g, 1-h oral glucose challenge test; if the result of this screening test was abnormal (glucose ≥7.8 mmol/l or 140 mg/dl), a 100-g, 3-h oral glucose tolerance test (OGTT) was performed in the following 1–2 weeks. Women were diagnosed with GDM if two or more of the 100-g OGTT glucose levels exceeded the following cut-off values based on the criteria of the American Diabetes Association: fasting, ≥5.3 mmol/l (≥95 mg/dl); 1 h, ≥10.0 mmol/l (≥180 mg/dl); 2 h ≥8.6 mmol/l (≥155 mg/dl); and 3 h, ≥7.8 mmol/l (≥140 mg/dl). Data concerning age, parity, history of diabetes during previous pregnancies and family history of diabetes were collected from the patients' medical records. The study was approved by the Internal Review Board of the Royan Institute. All patients signed a consent form on their initial visit giving permission to use their results anonymously in future studies.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences Version 16.0.0 (SPSS Inc., Chicago, IL, USA). Categorical and continuous variables were compared between the IVF/ICSI, IUI and spontaneous pregnancy groups using Chi-squared test and analysis of variance, respectively. Multiple comparisons were performed using Tukey's adjustment. Descriptive statistics are presented as mean ± standard deviation and percentage. Multivariate logistic regression using the Hosmer–Lemeshow algorithm was applied to evaluate the association between the mode of conception and the incidence of GDM after adjusting for potential confounding variables. Confounding variables were included if they satisfied the criteria of changing the −2 log likelihood by at least 3.84. This resulted in a final model that included age, pre-pregnancy BMI and progesterone support during the luteal phase. The anticipated difference in the incidence of GDM between spontaneous and ART pregnancies was 10%. At least 75 cycles were needed in each group to prove a difference of 10% with a power of 80%, assuming Type I error of 0.05.

Results

The medical records of 215 women who conceived spontaneously and 145 women who conceived following ART were evaluated from September 2011 to October 2012. The ART group was further subdivided into IVF/ICSI and IUI groups for better comparison of the incidence of GDM.

As expected, women's age, age at menarche and nulliparity were higher in the two ART groups compared with the spontaneous pregnancy group. More women had irregular menses in the IUI group (18%) compared with the IVF/ICSI (9.5%) and spontaneous pregnancy (4.7%) groups ($p = 0.005$). Significant differences in pre-pregnancy BMI and weight gain were found between the ART and spontaneous pregnancy groups (Table 1). The incidence of GDM was significantly higher in the IVF/ICSI (43%) and IUI groups (26%)

Table 1
Characteristics of women in the spontaneous pregnancy, in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and intra-uterine injection (IUI) groups.

Variables	Spontaneous pregnancy group ($n = 215$)	IVF/ICSI group ($n = 95$)	IUI group ($n = 50$)	p-Value
Age (years)	26.6 ± 5.8	31.3 ± 4.9	29.4 ± 5.8	<0.001[a]
Age at menarche (years)	12.6 ± 1.4	13.3 ± 1.5	13.5 ± 2.3	0.001[b]
Regular menses, n (%)	205 (95.3)	86 (90.5)	41 (82)	0.005
Pre-pregnancy body mass index (kg/m^2)	27.0 ± 3.9	25.4 ± 4.6	26.0 ± 3.3	0.004[c]
Weight gain in pregnancy (kg)	10.7 ± 2.5	11.5 ± 2.6	11.9 ± 2.0	0.004[d]
Nulliparous, n (%)	84 (39.1)	66 (69.5)	30 (60)	<0.001
Incidence of pregnancy-induced hypertension, n (%)	14 (7.2)	20 (21.0)	7 (14)	0.01
Incidence of gestational diabetes mellitus, n (%)	22 (10.2)	41 (43.1)	13 (26)	<0.001

Results expressed as mean ± standard deviation unless otherwise indicated.
[a] IVF/ICSI vs spontaneous conception ($p < 0.001$), IUI vs spontaneous conception ($p = 0.005$), IVF/ICSI vs IUI ($p = 0.1$).
[b] IVF/ICSI vs spontaneous conception ($p = 0.007$), IUI vs spontaneous conception ($p = 0.007$), IVF/ICSI vs IUI ($p = 0.8$).
[c] IVF/ICSI vs spontaneous conception ($p = 0.004$), IUI vs spontaneous conception ($p = 0.25$), IVF/ICSI vs IUI ($p = 0.66$).
[d] IVF/ICSI vs spontaneous conception ($p = 0.04$), IUI vs spontaneous conception ($p = 0.01$), IVF/ICSI vs IUI ($p = 0.6$).