# Gestational diabetes in IVF and spontaneous pregnancies

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## Abstract

**OBJECTIVE:** Increasing number of pregnancies resulting from *In vitro* Fertilisation (IVF) combined with increased awareness of Gestational Diabetes Mellitus (GDM) – related morbidity calls for research on possible differences in pregnancy outcomes between IVF and non-IVF GDM complicated pregnancies. The aim of this study was to compare GDM – affected pregnancies, both resulting from IVF and conceived without medical intervention with regards to maternal data, fetal biometry and neoanatal outcomes.

**METHODS:** We used our Clinic's databases to retrospectively identify 36 women who had successful IVF and developed GDM during the course of their singleton pregnancy (IVF group) and 137 non-IVF women with GDM (non-IVF group). They were matched according to age, pre-pregnancy BMI and none had the history of diabetes mellitus before their pregnancies. We compared the maternal characteristics, course of pregnancy and neonatal outcome.

**RESULTS:** The weight gain until the diagnosis of GDM in both non-IVF and IVF groups of women was not significantly different (9.81±4.37 vs 10.0±4.8 kg, $p$=0.8 respectively) with similar time at which they came under the specialist GDM care (29±4.0 vs 28±4.5 wks, $p$=0.42,). When analyzing first trimester fasting glucose levels we found it to be significantly higher in IVF group (89±16.2 vs 83±11.3 mg/dl, $p$=0.04). Second trimester oral glucose tolerance test (OGTT) results and glucose levels during GDM treatment did not differ between the groups. No changes were noted in investigated fetal and neonatal variances: 3rd trimester AC, it's percentile and neonatal birth weight (3 460±641 vs 3 200±440 g, $p$=0.22).

**CONCLUSIONS:** GDM among women after *in vitro* fertilisation is characterised by higher first trimester fasting glucose levels. Early diagnostic intervention in IVF pregnancies is specially needed.

ORIGINAL ARTICLE

## INTRODUCTION

Increasing number of pregnancies resulting from *in vitro* fertilisation (IVF) made researgers to compare the outcomes of pregnancies after infertility treatment. It seems that IVF pregnancies have higher risk of developing complications as preeclampsia (PE), preterm delivery, low birthweight, gestational diabetes (GDM) and higher perinatal mortality (Jackson *et al.* 2004). GDM risk factors such as age, multiple pregnancy and obesity are very often seen among IVF procedure participants. The one of most common endocrine disorders affecting fertility is polycystic ovary syndrome (PCOS). These patients have additional risk of developing carbohydrate intolerance during pregnancy and in the future (Boomsma *et al.* 2006). Fetal malnutrition resulting in hyperinsulinemia may affect neuroendocrine systems regulating body weight and carbohydrate metabolism in the offspring. The aim of this study was to compare GDM – affected pregnancies, both resulting from IVF and conceived without medical intervention with regards to maternal data, fetal biometry and neonatal outcomes. We hypothesized that GDM among the IVF patients develops earlier in pregnancy and it requires more intensive treatment.

## MATERIALS AND METHODS

We used database of 1st Department of Obstetrics and Gynaecology, Medical University of Warsaw to retrospectively identify 36 women who had successful IVF and developed GDM during the course of their singleton pregnancy (IVF group) and 137 non-IVF women with GDM (non-IVF group). The women were recruited from patients of 1st Clinic of Obstetrics and Gynaecology. An indication for *in vitro* procedure was unknown cause of infertility (19.4%), PCOS (16.7%), tubal occlusion (22.2%), male infertility (30.6%), endometriosis (11.1%). 4 (11.1%) patients conceived after ICSI (intracytoplasmic sperm injection) and 32 (88.9%) underwent conventional IVF.

Before the initiation of the study patients were informed about the study and all of them provided informed consent. Patients with pre-pregnancy diabetes, glucose intolerance or treated with hypoglycemic agents (e.g. metformin in PCOS) were excluded from the study. During the first pregnancy visit their weight, height and blood pressure were measured. All the participants had fasting plasma glucose measurement in the first trimester of pregnancy. GDM was diagnosed on a basis of fasting glucose (results above 125 mg/dl, twice measured) or 75 gram oral glucose tolerance test (OGTT). The cut-off values for OGTT were: fasting glucose of 100 mg/dl, 1-h 180 mg/dl, and 2-h 140 mg/dl. GDM was diagnosed by one or more abnormal values. The OGTT testing in the study group was performed on average during 27.8±3.8 week of gestation; in non IVF group – 27.6±6.9. All GDM women were put on a diabetic diet consisting 40% carbohydrate, 40% fat and 20% protein. They were equipped with glucometers (Optium Xido, Abbott) and were monitoring their blood glucose 4 times a day: fasting and 1 hour after each main meal. The diet should have assured normal glucose values: fasting <100 mg/dl; postprandial <140 mg/dl and during the night 60–90 mg/dl. If the targeted values of glucose couldn't be reached with the diet, insulin treatment was initiated (8 patients in IVF group – 22.2%, 26 patients in non-IVF group – 19%). Intermediate-acting biosynthetic human insulin (Insulatard, Novo Nordisk) was used to normalize fasting glucose and short acting insulin analog – insulin aspart – before main meals (Novo Rapid, Novo Nordisk).

The data concerning age, parity, history of diabetes during previous pregnancies and family history of diabetes were collected from the patients medical records.

For statistical analysis t-test was used to compare means of variances with normal distribution and Wilcoxon W test to compare medians of the rest of the variances. Data are given as means ± SD for age, BMI (body mass index), weight gain, birth weight and AC (abdominal circumference) percentile and medians ± interquartile range for time of pregnancy, AC and fasting glucose.

## RESULTS

Women in IVF group were matched according to parity, age and pre-pregnancy BMI (Table 1). Both non-IVF and IVF groups had similar age and pre – pregnancy BMI (31.7±4.43 vs 33.19±4.03 years, $p$=0.12 and 24.2±4.51 vs 25.88±3.96 kg/m$^2$, $p$=0.1, respectively).

As can be seen in Table 1, the weight gain in both groups of women was not significantly different. At the end of pregnancy all the women were about 10 kg heavier than before pregnancy (9.81±4.37 in non-IVF vs 10.0±4.8 kg in IVF group, $p$=0.8). The IVF and non-IVF group didn't differ concerning the time at which they came under specialist GDM care (29±4.0 vs 28±4.5 wks, $p$=0.42, respectively).

When analyzing first trimester fasting glucose levels we found it to be significantly higher in IVF group (89±16.2 vs 83±11.3 mg/dl, $p$=0.04) (Table 2).

No significant differences between the groups were revealed in OGTT results (Table 2).

No changes in investigated fetal and neonatal variances were noted: 3rd trimester AC (259.4±38 in non-IVF vs 267±19.5 mm in IVF group, $p$=0.35 ), it's percentile (65.3±30 vs 70.5±32.3, respectively, $p$=0.62) (Table 3). Although mean neonatal birth weight in IVF group was lower (3 200±440 g vs 3 460±641 g in non-IVF group) the difference didn't reach statistical significance ($p$=0.22).

Women after IVF developed preeclampsia more often than in non-IVF group (8.3% vs 3.6%, $p$=0.04).

Most of the infants in IVF group (79%) were delivered by cesarean section, whereas in non-IVF group only 33.9%. There were no significant differences in

frequency of neonatal complications between the two groups (Table 4).

## DISCUSSION

Pregnancies after *in vitro* fertilisation are at higher risk of perinatal complications such as spontaneous preterm delivery, preeclampsia, gestational diabetes. It is associated with the higher odds of perinatal mortality, low birth weight and small for gestational age (Jackson *et al.* 2004, Wang *et al.* 2005, Dhont *et al.* 1999, Mamam *et al.* 1998, Wiser *et al.* 2005). There are two hypothetic causes for higher rate of GDM after *in vitro* fertilisation. One is a higher incidence of PCOS among infertile women. In PCOS women physiological, pregnancy-induced peripheral insulin resistance is superimposed on PCOS-related insulin resistance existing in 25–70% patients (Legro *et al.* 2004). Two meta-analyses of pregnancy outcomes in PCOS women found them to be in a higher risk of developing GDM when compared to general population (OR-2.94; OR-2.89) (Boomsma *et al.* 2006, Toulis *et al.* 2009). But what is interesting, Kashanian *et al.* (2008) showed that PCOS – related obesity is a factor contributing to higher GDM prevelance. In their research, regarding body mass index, PCOS didn't have a significant relation to GDM. The same conclusion was reached by Haakova *et al.* They found no differences in GDM prevalence between PCOS and healthy, age and weight-matched controls (Haakova *et al.* 2003). Dokras reported significant, linear trend for risk of gestational diabetes among obese women after IVF with increasing BMI (Dokras *et al.* 2006). Li *et al.* (2010) showed that GDM women with PCOS are more likely to have a history of infertility diagnosis and treatment when compared to other GDM subjects. In our study the PCOS was diagnosed in 16.7% of IVF group and therefore PCOS can not be an explanation for GDM in patients after IVF. Moreover, our two groups, IVF and non-IVF were weight-matched, so we can exclude the impact of BMI on the results.

*In vitro* fertilisation is also associated with significantly higher risk of preeclampsia (Jackson *et al.* 2004). In our study the increase in the incidence of PE in IVF group was shown. Nowadays there is widely discussed the role of insulin resistance in the pathophysiology of PE (Morteza *et al.* 2011, Hauth *et al.* 2011, Lindsay *et al.* 1989; Vambergue *et al.* 2002;). It is suggested that infertile women, not only PCOS ones, are characterised by higher level of insulin resistance, and this may be the cause of GDM and PE development. It is evident that further studies on the insulin resistance in pregnant women after IVF are justified.

In our study we compared women with GDM-complicated pregnancies who had successful IVF with GDM women who conceived spontaneously. We hypothesized that GDM among the IVF women can have a different course. Our results indicate that GDM women after IVF are characterised by higher first trimester fasting glucose levels. We found no differences between second trimester OGTT results, time of GDM diagnosis, percentage of insulin therapy or neonatal birth weight. We can suspect that higher first trimester fasting glucose can be a result of a higher incidence of latent carbohydrate intolerance before pregnancy. It may indicate that

**Tab. 1.** Patient characteristics.

| | Non-IVF (n=137) | IVF (n=36) | *p*-value |
|---|---|---|---|
| Age [years] | 31.7 ± 4.43 | 33.19 ± 4.03 | ns |
| Height [m] | 1.66 ± 0.07 | 1.64 ± 0.02 | ns |
| Prepregnancy weight [kg] | 70.09 ± 4.51 | 25.88 ± 3.96 | ns |
| Prepregnancy BMI [kg/m$^2$] | 24.2 ± 0.73 | 23.15 ± 0.56 | ns |
| Weight gain in pregnancy [kg] | 9.81 ± 4.37 | 10.0 ± 4.8 | ns |
| Nulliparous | 91.2% | 91.7% | ns |
| Time of delivery [hbd] | 38.4 ± 1.5 | 37.9 ± 1.8 | ns |

**Tab. 2.** First trimester fasting glucose levels and OGTT results in non-IVF and IVF group (results expressed as mean ± fault).

| | Non-IVF (n=137) | IVF (n=36) | *p*-value |
|---|---|---|---|
| I$^{st}$ trimester fasting [mmol/l] | 4.61 ± 0.63 | 4.94 ± 0.9 | *p*=0.04 |
| OGTT 0h [mmol/l] | 4.86 ± 0.73 | 4.99 ± 0.84 | ns |
| OGTT 1h [mmol/l] | 9.64 ± 0.66 | 9.79 ± 0.7 | ns |
| OGTT 2h [mmol/l] | 8.33 ± 0.57 | 8.55 ± 0.74 | ns |

**Tab. 3.** Fetal biometry in third trimester and neonatal weight and lenght in non-IVF and IVF group (results expressed as mean ± fault).

| | Non-IVF (n=137) | IVF (n=36) | *p*-value |
|---|---|---|---|
| BPD [mm] | 77.7 ± 4.4 | 74.9 ± 8.2 | ns |
| AC [mm] | 259.4 ± 38 | 267 ± 19.5 | ns |
| FL [mm] | 58.4 ± 5.2 | 56.1 ± 6.3 | ns |
| Birth weight [g] | 3460 ± 641 | 3200 ± 440 | ns |
| Birth lenght [cm] | 54.8 ± 4.2 | 53.2 ± 3.3 | ns |

**Tab. 4.** Neonatal complications in non-IVF and IVF group.

| | Non-IVF (n=137) | | IVF (n=36) | | *p*-values |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Apgar score < 7 | 1 | 0.7% | 0 | 0% | ns |
| Mild hypoglicemia | 7 | 5.1% | 2 | 5.6% | ns |
| Severe hypoglicemia | 0 | 0% | 0 | 0% | ns |
| Jaundice requiring treatment | 9 | 6.6% | 2 | 5.6% | ns |
| Infection | 1 | 0.7% | 1 | 2.8% | ns |

patients eligible for IVF and pregnant after IVF treatment require particularly precise diagnosis of carbohydrate intolerance. It may be the group that could benefit from introduction of suggested after HAPO study fasting glucose cut-off value of 93 mg/dl for diagnosis of GDM (The HAPO Study Cooperative Research Group 2008). It is indicated that higher first trimester fasting glucose levels, considered to be within the nondiabetic range, increase the risk of adverse pregnancy outcomes such as LGA (large for gastational age), macrosomia and primary cesarean section (Riskin-Mashiiah *et al.* 2009). Fasting plasma glucose is easy, inexpensive and reliable laboratory test. Detection of women at higher risk on the basis of this test allows earlier intervention. These women, in preparation for the *in vitro* fertilisation and during first half of the pregnancy, should be encouraged to obey dietary guidelines, exercise and, in some cases, to lose weight. It can lower insulin resistance, lower the incidence of GDM in second half of pregnancy and have positive effect on pregnancy outcome. Early detection and treatment of carbohydrate intolerance in pregnancy is proved to have positive effect on maternal and fetal outcomes (Bartha *et al.* 2003, Seshian *et al.* 2008). Dietary intervention and physical activity in pregnant women after IVF can prevent excessive weight gain during pregnancy, development of GDM (Dempsey *et al.* 2004) and preeclampsia (Weissgerger *et al.* 2006).

REFERENCES


1 Australian *in vitro* fertilisation Collaborative Group (1985). High incidence of preterm births and early losses in pregnancy after *in vitro* fertilisation. BMJ. **291**: 1160–1163.
2 Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R (2003). Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications. Eur J Obstet Gynecol Reprod Biol. **109**: 41–44.
3 Boomsma CM, Eijkemans MJC, Hughes EG. Visser GH, Fauser BC, Macklon NS. (2006). A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Human Reproduction. **12**: 673–683.
4 Dempsey JC, Butler CL, Sorensen TK, Lee IM, Thompson ML, Miller RS et al (2004). A case-control study of maternal recreational physical activity and risk of gestational diabetes mellitus. Diabetes Res Clin Pract. **66**: 203–215.
5 Dhont M, De Sutter P, Ruyssinck G, Martens G, Bekaert A. (1999). Perinatal outcome of pregnancies after assisted reproduction: a case-control study. Am J Obstet Gynecol. **181**: 688–695.
6 Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. (2006). Obstetric outcomes after *in vitro* fertilisation in obese and morbidly obese women. Obstet Gynecol. **108**: 61–69.
7 Haakova L, Cibula D, Rezabek K, Hill M, Fanta M, Zivny J (2003). Pregnancy outcome in women with PCOS and in controls matched by age and weight. Hum Reprod. **18**: 1438–1441.
8 Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ et al (2011). Maternal insulin resistance and preeclampsia. Am J Obstet Gynecol. **204**: 327 e1–6.
9 Jackson RA, Gibson KA, Croughan MS (2004). Perinatal outcomes in singletons following *in vitro* fertilisation: a meta-analysis. Obstet Gynecol. **103**: 551–63.
10 Kashanian M, Fazy Z, Pirak A (2008). Evaluation of the relationship between gestational diabetes and a history of polycystic ovarian syndrome. Diabetes Res Clin Pract. **80**: 289–92.
11 Legro RS, Castracane VD, Kauffman RP (2004). Detecting insulin resistance in polycystic ovary syndrome: puproses and pitfalls. Obstet Gynecol Surv. **59**: 141–154.
12 Li G, Fan L, Zhang W, Huang X (2010). Metabolic parameters and perinatal outcomes og gestational diabetes mellitus in women with polycystic ovary syndrome. J Perinatal Med. **38**: 141–6.
13 Lindsay MK, Graves W, Klein L (1989). The relationship of one abnormal glucose tolerance test value and pregnancy complications. Obstet Gynecol. **73**: 103–6.
14 Mamam, Lunenfeld E, Levy A, Vardi H, Potashnik G (1998). Obstetric outcome of singleton pregnancies conceived by *in vitro* fertilisation and ovulation induction compared with those conceived spontaneously. Fertil Steril. **70**: 240–5.
15 Morteza A, Abdollahi A, Bandarian M (2011). Serum nitric oxide syntheses and lipid profile of the mothers with IUGR pregnancies uncomplicated with preeclampsia. Does insulin resistance matter? Gynecol Endocrinol. (Epub, in press)
16 Riskin-Mashiiah S, Younes G, Damti A, Auslender R (2009). First-trimester fasting hyperglycemia nad adverse pregnancy outcomes. Diabetes Care. **32**: 1639–1643.
17 Seshian V, Cynthia A, Balaji V, Balaji MS, Ashalata S, Sheela R (2008). Detection and care of women with gestational diabetes mellitus from early weeks of pregnancy: results in birth weight of newborn babies appropriate for geatational age. Diabetes Res Clin Pract. 199–202.
18 The HAPO Study Cooperative Research Group (2008). Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. **19**: 1991–2002.
19 Toulis KA, Goulis DG, Kolibianakis EM, Venetis CA, Tarlatzis BC, Papadimas I (2009). Risk of gestational diebetes mellitus in women with polycystic ovary syndrome: a systematic review and meta-analysis. Fertil Steril. **92**: 667–77.
20 Vambergue A, Nuttens MC, Goeusse P, Biausque S, Lepeut M, Fontaine P (2002). Pregnancy induced hypertension in women with gestational carbohydrate intolerance: the diagest study. Europ J Obstet Gynecol Reprod Med. **102**: 31–35.
21 Weissgerber TL, Wolfe LA, Davies GA, Mottola MF (2006). Excercise in the prevention and treatment of maternal-fetal disease; a review of the literature. Appl Physiol Nutr Metab. **31**: 661–674.
22 Wiser A, Levron J, Kreizer D, Achiron R, Shrim A, Schiff E (2005). Outcome of pregnancies complicated by severe ovarian hyperstimulation syndrome (OHSS): a follow-up beyond the second trimester. Hum Reprod. **20**(4): 910–914.