

# Treatment of Type 2 diabetes mellitus case leading to successful IVF pregnancy and birth outcome.

Tomomi Hashimoto<sup>1</sup>, Akira Nakabayashi<sup>1</sup>, Keiko Yanagisawa<sup>1</sup>, Chihiro Toma<sup>1</sup>, Yu Horibe<sup>1</sup>, and Tsutomu Tabata<sup>1</sup>

<sup>1</sup>Tokyo Women's Medical University

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## Abstract

In type 2 diabetes patients, attempting oocyte retrieval for egg cryopreservation without having established glycemic control does not yield good results. Strict dietary treatment and appropriate insulin administration is the best way to pregnancy.

[Names of the authors]

Tomomi Hashimoto<sup>a</sup>, Akira Nakabayashi<sup>a</sup>, Keiko Yanagisawa<sup>b</sup>, Chihiro Toma<sup>a</sup>, Yu Horibe<sup>a</sup>, Tsutomu Tabata<sup>a</sup>

[Title]

Treatment of Type 2 diabetes mellitus case leading to successful IVF pregnancy and birth outcome.

[Affiliations and addresses of the authors]

<sup>a</sup> Department of Obstetrics and Gynecology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

<sup>b</sup> Diabetes Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

[Corresponding author details]

Akira Nakabayashi

E-mail: [nakabayashi.akira@twmu.ac.jp](mailto:nakabayashi.akira@twmu.ac.jp)

8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Phone: +81-3-3353-8111

Fax: +81-3-5269-7619

[Key Clinical Message]

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[Abstract]

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## [Keywords]

Hyperglycemia

Insulin therapy

In vitro fertilization (IVF)

Type 2 diabetes mellitus

Obesity

Oocyte retrieval

## [Introduction]

It is not uncommon for obese diabetic patients with irregular menstruation and ovulation to seek fertility treatment in order to have a baby. Hyperglycemia during pregnancy increases the frequency of complications such as gestational hypertension, premature birth, stillbirth, and shoulder dystocia associated with delivery of an oversized baby, and may be a factor in congenital malformations of the baby. Therefore, it is imperative to improve blood glucose levels before pregnancy is attempted. Pregnancies complicated by obesity also increase the incidence of issues such as gestational hypertension and thrombosis, as well as perinatal problems such as increased necessity of cesarean section, and increased instance of blood loss during delivery. On the other hand, by performing in vitro fertilization (IVF), fertilized eggs obtained before weight loss and blood glucose improvement can be frozen, and thawed embryos can be transferred after weight and blood glucose levels are improved. While it is possible to avoid the decline in fertility associated with aging, the effectiveness of this method has not been clinically verified.

In this case study, at the patient's insistence, oocyte retrieval was performed at a time when blood glucose levels and body weight were not yet under control. However, pregnancy and delivery were ultimately achieved with an oocyte obtained after control had been established. For each of the three oocyte retrieval procedures, we noted and compared the amount of gonadotropin used, number of oocytes retrieved, the fertilization rate, and the number of resulting frozen embryos, along with the changes in blood glucose levels and body weight.

## [Case Report]

A 38-year-old married woman, diagnosed with type 2 diabetes mellitus (HbA1c: 9.0%) and hypertension at the age of 35, was prescribed oral hypoglycemic and antihypertensive medication for the condition. No diabetes-related complications such as retinopathy, nephropathy, or neuropathy were observed. When she visited her previous doctor with complaints of irregular menstruation and desire to have a baby, transvaginal ultrasonography showed endometrial thickening, and she was referred to our hospital because atypical endometrial hyperplasia was suspected after performing total endometrial curettage. According to the endometrial cytology performed at our hospital this case was categorized atypical endometrial cells of undetermined significance, and the endometrial histology showed no signs of malignancy. The histological specimen from the previous doctor was re-examined and our diagnosis was suspected endometrial hyperplasia without atypia. The results of blood tests performed on the 19th day of the menstrual cycle, this showed luteinizing hormone(LH) 6.9 mIU/ml, follicle stimulating hormone 7.1 mIU/ml, estradiol 41.4 pg/ml, and progesterone <0.2 ng/ml, indicating irregular menstruation associated with an ovulation disorder. As for her diabetes, her HbA1c, which had been around 7%, had risen to the 8% range after being prescribed Metformin Hydrochloride and selective Dipeptidyl Peptidase-4 inhibitors. The patient was referred to the Diabetes Center at our hospital because her HbA1c was not under control despite the change to multiple daily injection. A physical examination was performed at the patient's first visit to the Diabetes Center, and the following metrics were recorded; height of 167 cm, weight of 120 kg, Body Mass Index(BMI) of 43.0, and an HbA1c of 8.9%.

The patient, who had been diagnosed with suspected endometrial hyperplasia without atypia in our hospital, wanted to achieve an early pregnancy, and strongly desired oocyte retrieval as soon as possible, and prior

to glycemic control being established. The patient's anti-Mullerian hormone reading was 2.16 ng/ml. For the first oocyte retrieval performed before her admission for diabetes management, ovarian stimulation with Clomiphene Citrate and human menopausal gonadotropin(hMG) was performed and a total of 3,300 IU of hMG was administered. Ten follicles were aspirated, two oocytes obtained, and one viable embryo was achieved and subsequently frozen (Table 1). Since the patient requested more oocyte retrievals, a second oocyte retrieval procedure was performed after confirming that there were no residual follicles during menstruation. Her blood glucose level and body weight were similar to that when the first oocyte retrieval was conducted. This time, the antagonist method of ovarian stimulation was used, and a total of 3,600 IU of hMG was administered. On this occasion, eight follicles were aspirated, three oocytes acquired, and one viable embryo frozen (Table 1).

The patient was then admitted to the Diabetes Center, where she was placed on a 1200 kcal/day diet, and her insulin dose adjusted. Her fasting blood glucose level, which had been over 140 mg/dl, decreased to less than 100 mg/dl, and her 2-hour postprandial level, which had been around 200 mg/dl, decreased to less than 140 mg/dl. During the 11 days of hospitalization, HbA1c decreased to 7.0% by the following month (Fig. 1A). However, weight loss was deemed unsatisfactory, reducing from 120 to 117 kg only (Fig. 1B). Nevertheless a third oocyte retrieval procedure was performed after discharge. This time flare protocol was used for ovarian stimulation, and a total of 3,600 IU of hMG was administered. Eight follicles were aspirated, six oocytes acquired, and five viable embryos frozen (Table 1). After the patient's weight was reduced to 107 kg, a frozen embryo (10cells, +few fragments) obtained from the second oocyte retrieval procedure was thawed and transferred during the HRT cycle, but did not result in pregnancy. The pregnancy was subsequently achieved by transferring an embryo (early blastocyst) obtained from the third oocyte retrieval procedure. Tight glycemic control was maintained with insulin treatment throughout the pregnancy, and a baby boy weighing 3,144 g was delivered by cesarean section at 38 weeks and 2 days of the pregnancy. The patient gained 18kg during pregnancy, however, no maternal complications and no congenital abnormalities resulted.

#### [Discussion]

In this case, it was difficult for the patient to lose weight through her efforts alone, so she was admitted to hospital, where she was placed on a strict diet of 20 kcal/kg of her ideal weight, which triggered her weight loss. She eventually lost 13 kg. Weight loss alone was not sufficient to lower her blood glucose level, and hence insulin dosage was adjusted to achieve a good level after 11 days of hospitalization. Comparing the two oocyte retrieval procedures performed before hospitalization and the one after, there was no change in the total gonadotropin dosage in each case, which was because the weight loss was only 3 kg (about 3%), and hence there was relatively little change in body size. As for the fertilization rate, although it was low in the second oocyte retrieval procedure, overall it was satisfactory, and it was judged not have changed significantly from before and after hospitalization. However, the number of viable embryos appeared higher after hospitalization than before. From study on mice, there are reports that maternal-fetal diabetes affects oocyte maturation, development, and granulosa cell apoptosis[1], and that hyperglycemia decreases LH-luteinizing hormone /choriogonadotropin receptor expression[2], suggesting that improving blood glucose levels may have positively impacted oocyte retrieval in this case.

With regard to obesity and pregnancy rate, it has been reported that spontaneous pregnancy decreases linearly in infertile women with ovulation when BMI exceeds 29[3]. In addition, a meta-analysis reported that women with a BMI of 30 or more had a lower production rate after IVF (RR: 0.85) compared to women of normal weight[4]. However, a randomized study of obese infertile patients with a BMI of between 30 and 35 who underwent intensive weight loss by caloric restriction before IVF, reported an average weight loss of 9.44 kg but no improvement in reproduction rate[5]. Furthermore, bariatric surgery prior to IVF has already been performed, but it was also reported that there was no significant effect on reproductive rate[6]. In this case, the patient's weight loss was slow and her final BMI was 38, which was not ideal in terms of both perinatal and reproduction. However, permission for pregnancy was obtained from the perinatal physician at this facility, provided that she continued to manage her diet during pregnancy to minimize risk of perinatal

complications. Consequently, transfer of the thawed embryo was allowed to proceed.

[Conclusion]

In order to avoid an age-related decline in fertility, it is technically possible to perform oocyte retrieval early and cryopreserve the fertilized eggs. However, in diabetic patients, high blood glucose may affect the oocyte retrieval results, so it is desirable to perform oocyte retrieval after controlling blood glucose, in order to increase the likelihood of achieving pregnancy. In this case, the success of IVF may have been related to improvement in blood glucose levels through education on diabetes, including strict dietary treatment through hospitalization, and appropriate insulin administration.

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[Disclosures]

The authors declare no conflict of interest.

[Author contribution]

TH and AN: involved in preparing and writing the manuscript. KY, CT, YH, and TT: critically reviewed and approved the final manuscript version for submission. All authors: participated in the procedure and the management of the patient.

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[Table1] Results of oocyte retrieval prior to and post inpatient treatment for insulin adjustment

	Prior to treatment	Prior to treatment	post treatment
Gonadotropin Total Dose (IU)	3300	3600	3600
Number of follicles aspirated	10	8	8
Number of oocytes obtained	2	3	6
Number of fertilized eggs	2	1	6
Number of frozen embryos	1	2	5

[Figure legends]

Figure 1. (A)HbA1c Trends. (B)BMI Trends. The month of the first visit to the Diabetes Center at our hospital was set as month 0.

OR: oocyte retrieval, fET: frozen-thawed embryo transfer

