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著者名	HASHIMOTO Tomomi, NAKABAYASHI Akira, YANAGISAWA Keiko, TOMA Chihiro, HORIBE Yu, TABATA Tsutomu
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Is Fertility Treatment Prior to Establishing Glycemic Control Effective for Type 2 Diabetic Patients? A Case Study Comparing Outcomes Before and After Glycemic Control Is Established

Tomomi Hashimoto,¹ Akira Nakabayashi,¹ Keiko Yanagisawa,²
Chihiro Toma,¹ Yu Horibe,¹ and Tsutomu Tabata¹

¹Department of Obstetrics and Gynecology, Tokyo Women's Medical University, Tokyo, Japan

²Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan

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Some patients with type 2 diabetes desire egg retrieval for future embryo transfer, and would prefer the procedure to be performed prior to exerting glycemic control, which is technically possible. We experienced a case of a 38-year-old woman suffering from type 2 diabetes mellitus, hypertension, and severe obesity (body mass index 43) desiring early oocyte retrieval due to suspected endometrial atypia. Only 3 transferable embryos were obtained through two oocyte retrieval procedures before glycemic control was applied, whilst 5 transferable embryos were obtained in one egg retrieval cycle post inpatient treatment for insulin adjustment. The transfer of an embryo post-treatment resulted in delivery of a healthy full term child.

Keywords: hyperglycemia, insulin therapy, in vitro fertilization (IVF), type 2 diabetes mellitus, oocyte retrieval

Introduction

It is not uncommon for type 2 diabetic patients to seek fertility treatment in order to have a baby. Hyperglycemia during pregnancy increases the likelihood of complications such as gestational hypertension, premature birth, stillbirth, and shoulder dystocia associated with delivery of an oversized baby, and may also be a factor in congenital malformations of the baby. Therefore, it is imperative to improve blood glucose levels before pregnancy is attempted. However, some patients desire to have fertility treatment first, due to the length of time it

may take to achieve glycemic control, and the adverse consequences of aging in the interim. In recent years, the technique of embryo cryopreservation has been established, making it possible to retrieve oocytes before glycemic control for future embryo transfer.

In this case study with the subject suffering type 2 diabetes and obesity, and with suspected endometrial atypia, at the patient's insistence, oocyte retrieval was performed at a time when blood glucose levels 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 re-

Corresponding Author: Akira Nakabayashi, Department of Obstetrics and Gynecology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. nakabayashi.akira@twmu.ac.jp

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Table 1. Results of oocyte retrieval prior to and post inpatient treatment for insulin adjustment.

	Prior to treatment		Post treatment
Gonadotropin total dose (IU)	3,300	3,600	3,600
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	1	5

trieval 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 Presentation

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 embryos 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 1,200 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 (**Figure 1A**). However, weight loss was deemed unsatisfactory, reducing from 120 to 117 kg. That is, BMI only decreased from 43.0 to 42.0 (**Figure 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 (10 cells, +few fragments) obtained from the second oocyte retrieval

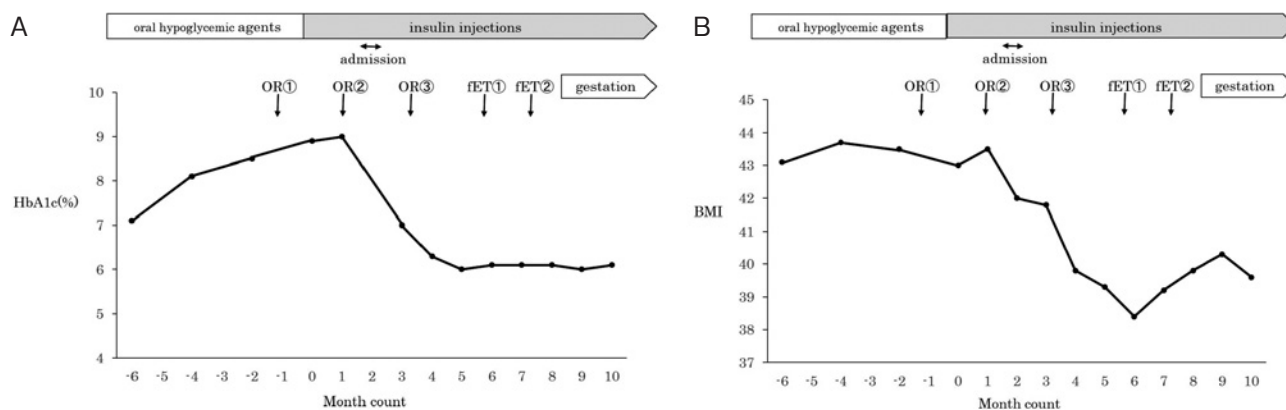


Figure 1.

(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.

procedure was thawed and transferred during the hormone replacement therapy 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. Blood glucose was stabilized through hospitalization for 10 days at 16 weeks of gestation, and self-monitoring of blood glucose level after discharge from hospital. To control blood pressure, one more antihypertensive drug was added at 24 weeks of gestation, but because this got elevated, the patient was again hospitalized at 35 weeks of gestation. Labor was induced at 38 weeks and 2 days of gestation, and a 3,144 g baby boy with an Apgar score of 8/9 was born by cesarean section after normal delivery was unsuccessful. The patient gained 18 kg during pregnancy, however, no maternal complications and no congenital abnormalities resulted.

Discussion

In this case, it was difficult for the patient to achieve glycemic control 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. This triggered her weight loss and she eventually lost 13 kg at the time of embryo transfer. Weight loss alone was not sufficient to lower her blood glucose level, and hence insulin dosage was adjusted to achieve a satisfactory 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 to have changed significantly from before and after hospitalization. However, the number of viable embryos appeared higher after hospitalization. From studies on mice, there are reports that maternal 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 and fertilization in this case. In humans, elevated fasting blood glucose has been reported to be associated with prolonged time to pregnancy.³ However, there have been no reports on the effects of hyperglycemia and hyperinsulinemia on oocyte retrieval.

With regard to obesity and pregnancy rate, it has been reported that spontaneous pregnancy decreases linearly in infertile women with ovulation when BMI exceeds 29.⁴ In addition, a meta-analysis reported that women with a BMI of 30 or more had a lower production rate after in vitro fertilization (IVF, RR 0.85) compared to women of normal weight.⁵ 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.⁶ Furthermore, bariatric surgery prior to IVF has already been performed, but it was also reported that there was no significant effect on reproductive rates.⁷ However, Pregnancies complicated by obesity have increased 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. In addition, weight loss reduces insulin resistance, therefore weight management is just as critical as glycemic control.

Although it cannot be determined with any certainty from a single case, it may indicate that in diabetic patients, high blood glucose may affect oocyte retrieval results. Hence, it may be desirable to perform oocyte retrieval after blood glucose is under control, in order to increase the likelihood of achieving pregnancy. In this particular 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.

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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Conflicts of Interest: The authors declare that they have no conflict of interest regarding the publication of this case report.

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All authors: participated in the procedure and the management of the patient.

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Ethical Approval: Not Applicable.

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