

Management of Pregnancy Achieved by Oocyte Donation to a Woman with 47,XXX and POF

Yusuke Shibuya¹, Yukihiro Terada^{2*}, Jin Kumagai²,
Yukiyo Kumazawa², Masatoshi Saito¹,
Tetsuro Hoshiai¹ and Nobuo Yaegashi¹

¹Department of Obstetrics and Gynecology, Tohoku University, Miyagi 980-8574, Japan

²Department of Obstetrics and Gynecology, Akita University, Akita 010-8543, Japan

Abstract: [Objective] To present a case of pregnancy achieved by oocyte donation abroad to a woman with 47,XXX and premature ovarian failure (POF). [Patient(s)] A 39-year-old woman, gravida 0, para 0, with 47,XXX, POF and hypertension, achieved pregnancy by donation of oocytes abroad, and consulted us for pregnancy management. Dichorionic diamniotic twin fetuses were observed by ultrasonography, and gestational diabetes mellitus (GDM) occurred at 12 weeks of gestation. One of the twins was diagnosed with intrauterine growth restriction (IUGR) at 24 weeks of gestation. Uterine contraction was frequently observed at 28 weeks of gestation. Brain sparing effect was seen in the IUGR fetus at 30 weeks of gestation. The IUGR fetus presented a non-reassuring fetal status (NRFS) at 32 weeks of gestation, therefore twins were delivered by Caesarean section. [Results] Neonate 1 weighed 1,754 g with an Apgar score of 9/10 (1/5 minutes). Neonate 2 weighed 950 g with an Apgar score of 7/8. Both did well. While GDM improved in three weeks, the patient's hypertension persisted after delivery. [Conclusion] This kind of case will increase in Japan due to the emergence of middlemen for oocyte donations. To prepare for them, it is necessary to further investigate mechanisms of complications in pregnancies achieved with donated oocytes.

Key words: Oocyte donation, 47,XXX, POF, IUGR, PIH

Introduction

According to the current consensus in medicine, oocyte aging determines the fecundity of the couple. From this point of view, it is clear that patients with infertility will increase because of the rising trend in age at the time of marriage. A premature ovarian failure (POF) patient who cannot produce an oocyte can hardly hope for pregnancy in Japan because oocyte donation (OD) is currently not approved. However, the demand for antenatal care after receipt of donated oocytes in Japan still exists due to the emergence of middlemen for oocyte donation. Pregnancy after oocyte receipt is different from ordinary pregnancy, because of higher maternal age, and the peculiar situation whereby a transplanted embryo is a complete allograft for the mother.

It has been speculated that younger patients with premature ovarian failure should have lower prevalence rate of pregnancy complication such as hypertension, glucose intolerance etc. than ordinary OD patients. We report the case of a POF patient who requested us to manage her antenatal care after OD, and this case indicates that young patients with POF with chromosome abnormalities might also experience those pregnancy complications.

Case Report

Course before oocyte donation

A 33-year-old Japanese female presented with secondary amenorrhea. She had married at 33 years of age, and had an unremarkable medical and clinical history. The menstrual cycle was regular from

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*To whom correspondence should be addressed.

e-mail: teraday@obgyn.med.akita-u.ac.jp

menarche (11 years old) to 20 years of age, but after that she became oligomenorrhea and by 32 years of age, she became amenorrhea. At initial examination, the uterus was thumb head size and we could not detect both ovaries. Furthermore, her serum follicle-stimulating hormone (FSH) level was 38.9 mIU/ml, luteinizing hormone (LH) level was 14.6 mIU/ml, prolactin level was 2.9 ng/ml, estradiol level was 24.4 pg/ml, and total testosterone level was 72.1 ng/dl. So, the diagnosis of POF was made. Also, sex chromosome disorder (47,XXX) became clear at karyotyping on peripheral white blood cells. In that analyses, 30 of cells were analyzed, and karyotype of all cells were 47, XXX. We explained to the patient that she had little hope of pregnancy because of POF and continued hormone replacement therapy. Hypertension was diagnosed at 35 years of age and antihypertensive medication was started.

Six years after the patient's initial presentation, at 39 years of age, she went to the USA to receive donated oocytes. She received two embryo implants, and on her return to Japan, she consulted us. We diagnosed dichorionic diamniotic twin pregnancy. At the patient's request, we conducted antenatal care at our hospital.

Course after oocyte donation

For hypertension, the patient was prescribed oral Labetalol hydrochloride 450 mg/day which controlled her hypertension. At 12 weeks of gestation, gestational diabetes mellitus (GDM) was diagnosed (for 75 g of GTT 0-60-120 min, 98-189-160 mg/dl) and we started insulin therapy (NovoRapid® 2-2-2 unit). Intrauterine growth restriction (IUGR) of one of the fetuses was found in the fetal growth evaluation by ultrasonography at 24 weeks of gestation. Subsequently, the head circumference grew, but extension of the femoral length was delayed, and the difference in the estimated body weights of both fetuses became worse (Figs. 1, 2). The patient's blood pressure increased from week 26 of gestation, and we added 20 mg/day of hydralazine hydrochloride to her medication. Nevertheless, the control was poor, so we changed the prescription to Labetalol hydrochloride 900 mg/day and methyl dopa 500 mg/day. Uterine contractions became remarkable from week 28 of gestation, and we started the administration of 20 mg/day of ritodrine hydrochloride with hospitalization with a diagnosis of threatened preterm labour. Brain sparing effect of the IUGR fetus was found by antenatal cerebral doppler findings at week 30 of gestation (Fig. 3).

At week 32⁺¹ of gestation, an emergency Cesarean

section was performed because of the non-reassuring fetal status (NRFS) of the IUGR fetus. The first baby (appropriate for gestational age (AGA) fetus) weighed 1,754 g with Apgar scores of 9 and 10 at 1 and 5 min, respectively. The second baby (IUGR fetus) weighed 950 g with Apgar scores of 7 and 8 at 1 and 5 min, respectively. It was a premature birth, but both babies did well and did not have any congenital anomalies. GDM improved in the three weeks after delivery, but hypertension persisted at about 140 mmHg (systolic blood pressure), and medication was continued.

Discussion

Pregnancy after receipt of a donated oocyte, maternal age, maternal POF and maternal sex chromosome disorder may have conferred independent risks to the various complications observed in this case.

This case had essential hypertension and changed for the worse at second trimester. This case is not PIH, but some hypertensive agents would exist. Wiggins *et al.* compared 50 cases of standard *in vitro* fertilization (STD-IVF; 37.7 ± 3.6 years old) with 50 cases of donor egg *in vitro* fertilization (DE-IVF; 41.9 ± 5.1 years old). Examining nulliparous patients only, 37.1% (13/35) of the DE-IVF group had pregnancy induced hypertension (PIH), whereas only 8.3% (3/37) of the STD-IVF group showed a similar diagnosis ($P < .003$). An analysis with multiple logistic regression of nulliparous patients found an odds ratios of 7.1 (95% CI, 1.4-36.7) for PIH in DE versus STD-IVF and an odds ratio of 1.0 (95% CI, 0.9-1.1) for maternal age [1]. Simchen *et al.* studied 125 cases of DE-IVF in mothers aged 40 or older. There were 42 cases carrying twins after DE-IVF (49.2 ± 4.3 years old) in the study group and they were compared with 417 control cases with twins (31.6 ± 6.5 years old). Incidences of PIH and GDM were 50% and 31% in the study group, whereas they were 9.1% and 7.3% in the control group ($P < 0.001$), respectively. However, incidences of PIH and GDM were 42% and 29% in 83 cases of DE-IVF carrying singletons (49.3 ± 4.7 years old), respectively, and there were no significant differences with the control group. Mean gestational age at delivery was lower for the study group compared with controls (35.2 ± 2.3 versus 35.7 ± 2.6 weeks). Simchen *et al.* suggested that maladaptation of the uterus to pregnancy because of uterine aging would explain the results [2]. They also compared 33 cases of older (50 years old or older) DE-IVF with 118 cases of younger (45-49 years old) DE-IVF. The incidence of PIH was 33% in the older group, whereas it was 27% in

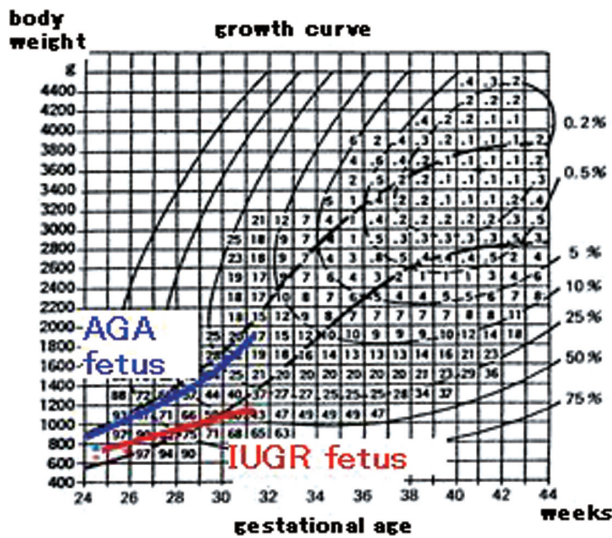


Fig. 1. Growth curves of both fetuses
Selective IUGR was found from week 24 of gestation and growth discrepancy with the other fetus increased.

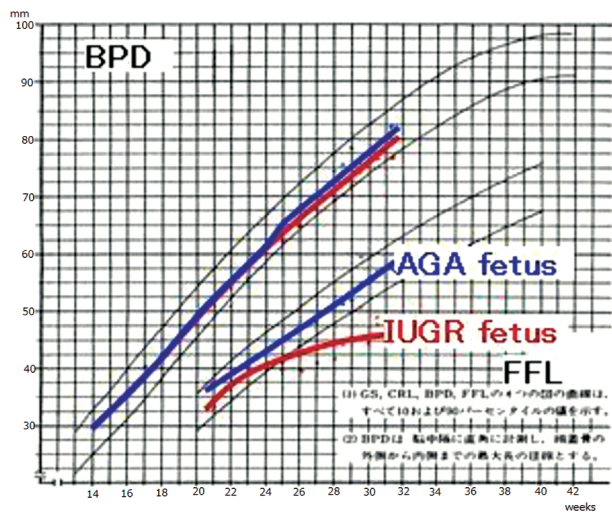


Fig. 2. Asymmetrical IUGR
The head circumference of the IUGR fetus grew, but extension of the femoral length was delayed.

the younger group ($P=0.55$) [3]. The study of Wiggins *et al.*, examining nulliparous patients, found an odds ratios of 7.1 for PIH in DE versus STD-IVF. Also, Simchen *et al.* found the non-adjusted odds ratio for PIH was 10.0 in the older versus younger patients with twin pregnancy. However, most of this increase in the odds ratio may be due to oocyte receipt because both groups achieved pregnancy after receipt of donated oocytes.

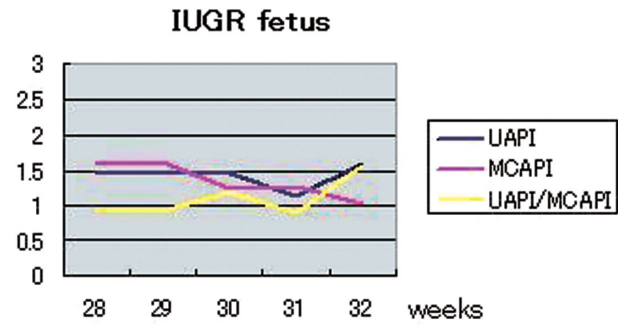


Fig. 3. Antenatal cerebral doppler findings of the IUGR fetus
Brain sparing effect was found in the IUGR fetus from week 30 of gestation.

According to some reports in Japan, PIH is frequently found during antenatal care after oocyte donation. All of the reported cases received oocytes abroad. According to Kuji *et al.*, three patients developed obstetric bleeding after oocyte donation. One case was placenta accreta, one case was unidentified bleeding after Cesarean section, and the other case was a cervical pregnancy. PIH did not occur in any of these three cases, therefore, they suggested the mechanisms of obstetric bleeding and PIH may different [4].

47,XXX is estimated to occur in one in approximately every 1,000 females and the incidence increases with maternal age [5]. Regarding the relationship between 47,XXX and physical abnormality, there is a report of a case with a 47,XXX showing urogenital abnormality or omphalocele [6]. However, in the follow-up of 17 cases of 47,XXX discovered by screening of newborns, only tall height and articulatory delay were reported and it was indicated that 47,XXX does not develop into serious disease [7–9]. A female with 47,XXX developed POF and autoimmune disease at 17 years old [10]. Some researcher speculated autoimmunity plays some role in pathologic manifestation of 47,XXX, like POF. However, some 47,XXX have normal fecundity and the chromosome of their baby was normal [11]. This phenomenon indicates clinical manifestation of 47,XXX is heterogeneous. Although it was speculated that younger patients with premature ovarian failure should have lower prevalence rate of pregnancy complication than ordinary OD patients, this case indicates those patients with premature ovarian failure with chromosome abnormalities might also experience those pregnancy complication. The above-mentioned follow-up study is still continuing in the USA and definitive conclusions about pregnancy in 47,XXX cases have yet to be reached.

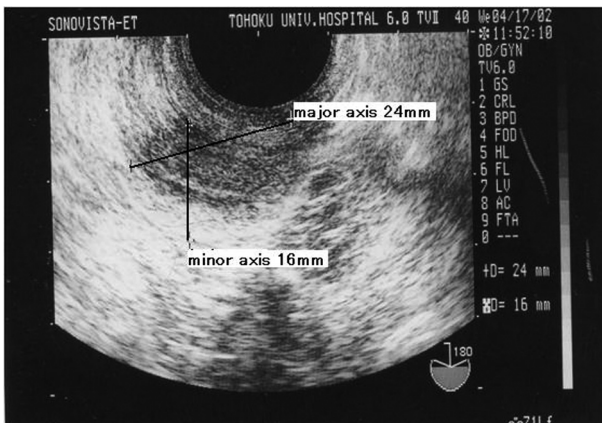


Fig. 4. Uterus at initial examination
The uterus at the initial examination was thumb-head size (24 mm*16 mm).

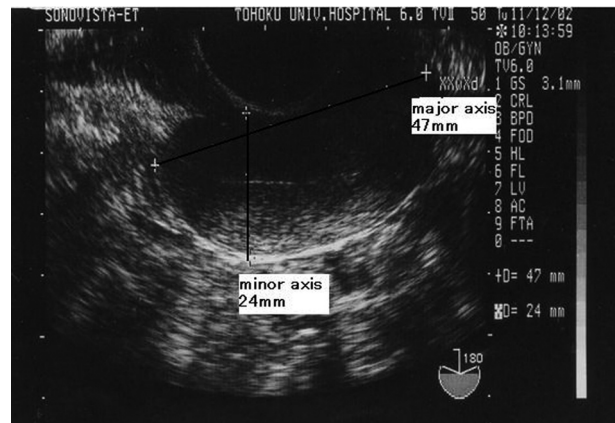


Fig. 5. Uterus after Kaufmann treatment
After Kaufmann treatment, the uterus size had grown (47 mm*24 mm).

We experienced a case of 47,XXX with POF. The associations between various factors and the pregnancy complications that occurred in this pregnancy are unknown. We think uterine size may have been one of the causes. The uterus at the initial examination was of thumb-head size, but after Kaufmann treatment, the uterus size increased in size, although its size at embryo transfer was still extremely small (Figs. 4, 5). In a small and restrictive uterine cavity, the placenta could become aplastic and PIH and IUGR would develop.

Conclusion

Cases receiving oocyte donations abroad and antenatal care or delivery in Japan will increase in the future. For such cases, we should recognize the increased risk of PIH or GDM, conduct frequent fetal monitoring to diagnose IUGR and threatened preterm labour and pay attention to postpartum abnormal bleeding. Also, it will be necessary to explain the anticipated risks to patients with infertility considering oocyte donation.

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