Successful outcome of a pregnancy derived from premature ovulation in a gonadotropin-releasing hormone (GnRH) antagonist protocol: a case report

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Abstract

Premature ovulation may occur during controlled ovarian stimulation. Usually, this is noticed and treatment is canceled before ovum pick up (OPU). In this case, a 24-year-old woman naturally conceived during the stimulation and OPU was successfully performed afterwards. Despite developing severe ovarian hyperstimulation syndrome, she delivered a healthy baby.

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Abstract

Premature ovulation may occur during controlled ovarian stimulation. Usually, this is noticed and treatment is canceled before ovum pick up (OPU). In this case, a 24-year-old woman naturally conceived during the stimulation and OPU was successfully performed afterwards. Despite developing severe ovarian hyperstimulation syndrome, she delivered a healthy baby.

Key words

gonadotropin-releasing hormone (GnRH) antagonist, ovarian hyperstimulation syndrome (OHSS), pregnancy, premature ovulation, premature LH surge

Key Clinical Message

In the gonadotropin-releasing hormone (GnRH) antagonist protocol, it is necessary to reinforce contraceptive guidance assuming that luteinizing hormone surge is not detected by measurement of serum level and ovulation is not suppressed by GnRH antagonist.

1 Introduction

Gonadotropin-releasing hormone (GnRH) antagonists are currently widely used for controlled ovarian stimulation (COS). GnRH antagonists have the advantage of preventing severe ovarian hyperstimulation syndrome (OHSS) by using GnRH agonists as the final oocyte maturation trigger instead of human chorionic gonadotropin (hCG), which has a long half-life[1,2].

Preventing premature ovulation (PO) completely is difficult. However, Wu et al.[3] reported three cases of pregnancy by oocyte retrieval from residual follicles after PO. Additionally, Vicdan et al.[4] reported five cases of PO that were converted from *in vitro* fertilization (IVF) to intrauterine insemination (IUI) and two became pregnant. In most cases of PO, it is noticed and the IVF cycle is canceled. Therefore, there have been few reports of successful cases of pregnancy after PO.

We report a case of spontaneous pregnancy due to PO in a GnRH antagonist protocol. No signs of a premature luteinizing hormone (LH) surge or PO were observed, despite monitoring LH levels and the follicle count during the COS. Additionally, luteal function was maintained even after the GnRH agonist trigger so the pregnancy continued, and a healthy live neonate was delivered.

2 Case presentation

2-1 First consultation for assisted reproductive technology

A 24-year-old woman, gravida 0, para 0 had no special medical history and a regular 28-day menstrual cycle. Her body mass index was 20.8 kg/m^2. After five cycles of timed intercourse and one cycle of IUI at another hospital, she did not become pregnant and decided to visit our hospital. Her anti-Mullerian hormone level was 5.34 ng/mL. After the first visit, IUI was performed for two cycles, but she did not become pregnant. The decision was then made to apply assisted reproductive technology (ART).

2-2 Clinical course of ART

COS with follicle-stimulating hormone (FSH) (gonal-f, follitropin-alpha, EMD serono, Japan) or human menopausal gonadotropin (hMG) (ferring, Ferring Pharma, Japan) were started on the cycle day (CD) 3 and GnRH antagonist ; cetrorelix acetate (cetrotide) from CD 14. The total duration of treatment was 20 days, with a total of 6625 units of FSH + hMG administered (Figure 1).

On the 19th day of stimulation, we decided to retrieve the oocytes (ovum pick-up [OPU]) 3 days later, and stimulation was continued until the 20th day. A final oocyte maturation trigger was performed with a GnRH agonist (leuprolide acetate [Lucrin]; AbbVie, Illinois, USA) (subcutaneous administration, 1 mg), and 35 hours later, the oocytes were retrieved with a transvaginal needle under venous anesthesia. A total of 31 oocytes (26 × meiosis-2 stage [M2], 2 × meiosis-1 stage [M1], 1 × germinal vesicle stage, and 2 × degenerated oocytes) were obtained. The unadjusted sperm volume was 3.2 mL, the motile sperm concentration was 5 M/mL, and the sperm motility was 17.9%, so insemination of the M2 oocytes was split. The fertilization result from intracytoplasmic sperm injection (ICSI) was 21 (12 × 2 pronuclear stage [PN], 1 × 1 PN, 5 × 3 PN, 3 × degeneration [Deg]) and that for conventional IVF was five (3 × 2 PN, 1 × 3 PN, 1 × Deg). Confirmation of fertilization showed 15 × 2 PN embryos and 1 × 1 PN embryo. Therefore, 8 × 2 PN embryos were cryopreserved and the remaining 7 × 2 PN and 1 × 1 PN embryos were cultured for blastocysts. Three blastocysts were formed by day 7 of culture (3AB, 4AA, 4BC by the Gardner classification).

2-3 Clinical course after the OPU

Abdominal pain began the day after the OPU, and the patient lost consciousness twice on the 3rd day after the OPU, so she went to a hospital. A large amount of ascites, bilateral ovarian swelling (right: 56 × 69 mm, left: 62 × 45 mm), a heart rate of 110 bmp, and blood pressure of 70/50 mmHg were observed at the time of admission. The patient was immediately hospitalized and diagnosed with hypovolemic shock and severe OHSS.

No abnormal findings were detected by head magnetic resonance imaging. A blood test showed the following: albumin level of 2.8 g/dL, creatinine 0.84 mg/dL, sodium 134 mEq/L, potassium 5.5 mEq/L, AST 44 U/L, ALT 20 U/L, WBC 15,300/μL, hemoglobin 18.7 g/dL, and Ht 54.3%. A heparin and dopamine drip infusion was administered.

Her ascites increased from the 8th day after the OPU (6th day of hospitalization), and a puncture and drainage procedure was performed twice. On day 11 after the OPU, transvaginal ultrasonography showed a 10-mm gestational sac (GS) in the uterus, and her blood hCG level was 6990 mIU/mL. She was then discharged from the hospital on the 17th day after the OPU without any increase in ascites. After discharge, the course of her pregnancy was uneventful, and she gave birth to a female neonate (3136 g) at 40 weeks+1. At a 1-month postnatal examination, the infant was healthy without complications.

3 Discussion

The definition of a premature LH surge differs depending on the study. In our case, if the definition of Kummer et al.[5] (LH levels [?] 10 mIU/mL and > 50% rise from baseline) was used, an accurate premature LH surge or ovulation could not be predicted or specified. Therefore, the spontaneous ovulation date of our case was estimated from two parameters, the GS and crown-rump length (CRL). If a 10-mm GS is detected at 11 days after the OPU and that day is defined as a menstrual age of 40 days[6], the estimated ovulation date is CD 9. The CRL was 15 mm 28 days after the OPU, and the estimated gestational age was 7 weeks+4, 8 weeks+2, and 9 weeks by 5, 50, and 95 percentile, respectively. Therefore, the estimated ovulation date was CD 8 (3–13)[6]. Because the natural menstrual cycle in our case was 28 days, this suggested that ovulation might have occurred earlier than it should have in a natural cycle.

If normal COS is in progress, early luteinization and follicular atresia will occur after a premature LH surge[7]. However, in our case, fertilization and implantation occurred after the presumed spontaneous ovulation day, and follicular development was observed after this time. A total of 31 oocytes were retrieved by using a GnRH agonist trigger.

A previous study reported that the outcome of luteal phase ovarian stimulation (LU) was higher than that for follicular phase ovarian stimulation (FO) regarding the total dosage of hMG, M2 rate[7], number of oocytes collected, fertilization rate, and the number of day 3 embryos[8]. Additionally, a study that compared FO only to FO + LU reported that the FO + LU group had a higher number of retrieved oocytes, M2 rate, and 2 PN rate[9]. Theoretically, continued stimulation after spontaneous ovulation is therefore possible for retrieving oocytes.

Although good results are obtained with LU, in this case, as a result of ICSI performed on 21 M2 oocytes in our case, 12 of 21 had 2 PN, but 5 had 3 PN. Higher peak estradiol levels, large oocyte yields, a high gonadotropin dose, and a lengthy stimulation procedure are considered to increase 3 PN[10,11]. Therefore, additional attention should be paid to stimulation after spontaneous ovulation.

4 Conclusion

In conclusion, because the mechanisms of ovulation and oocyte maturation remain unclear, strict monitoring and proper contraceptive guidance are important during COS using the antagonist method. When oocyte retrieval is performed in a natural pregnancy, the risk of developing severe OHSS and threats to life increase. Therefore, guidance for contraception during infertility treatment seems contradictory, but it must be strictly used.

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Conflicts of interest

The authors declare that they have no conflicts of interest regarding the publication of this case report.

Author Contributors

Daichi Inoue drafted the manuscript.

Yoshimasa Asada reviewed the manuscript.

Tomoko Ando reviewed the manuscript as an attending doctor of OHSS

Ethics approval and consent to participate

Informed consent was provided by the patient.

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ovulation period estimated from CRL

ovulation day estimated from GS size

GnRH agonist trigger

cycle day		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
days of stimulation		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
FSH		150	150																			
hMG				225	225	225	225	300	300	300	375	375	375	375	375	375	375	450	450	450	450	
low dose hCG														30	30	30	30	30	30	30	30	
antagonist													A		A		A		A			
Rt	1	6 x 5		7 x 6				12 x 10			16 x 13			23 x 22				32 x 27		47 x 27		
	2			6 x 5				11 x 10			14 x 14			25 x 19				32 x 26		40 x 28		
	3			6 x 5				12 x 9			14 x 11			22 x 21				27 x 27		37 x 21		
	4			5 x 5				10 x 8			13 x 11			20 x 20				24 x 24		30 x 24		
	f	5		6				12			9(2)			12(6)				12(9)		14(12)		
Lt	1	5 x 5		6 x 6				12 x 11			17 x 14			21 x 21				28 x 24		30 x 23		
	2			7 x 5				10 x 8			12 x 11			17 x 15				23 x 22		25 x 23		
	3			7 x 5				11 x 7			13 x 10			15 x 15				22 x 20		24 x 21		
	4							5 x 5			8 x 8			12 x 9				20 x 17		25 x 19		
	f	4		3				7			10(1)			11(3)				12(8)		14(10)		
EM		6.1		7.4				14.9			10.3			13.8				9.8		12.8		
FSH		8.7		8.8				12.5			17.8			23.9				21.4		23.2		
LH		7.3		2.9				5.4			2.4			0.9				<0.1		0.2		
E2		30.8		126				887			2002			4293				7956		10842		
hCG		<0.5																4.3		11.8		
P4																						