

# Direct intraperitoneal insemination in ovarian hyperstimulation cycles induced with gonadotropin-releasing hormone agonist

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## Summary

Direct intraperitoneal insemination (DIPI) is one of the least invasive strategies of assisted reproduction. Unexplained infertility, cervical factors and male sub-fertility are major indications for DIPI. This is a report of pregnancy that occurred as a result of a novel trial of DIPI, in which ovarian stimulation took place using a long gonadotropin-releasing hormone (GnRH) analogue and human menopausal gonadotropin (HMG) protocol in a patient who had been unsuccessfully treated with intrauterine insemination.

**Key words:** Direct intraperitoneal insemination; Hyperstimulation; Gonadotropin-releasing hormone agonist.

## Introduction

Direct intraperitoneal insemination (DIPI) was introduced as an alternative to gamete intrafallopian transfer (GIFT) [1], which is a more intensive, time consuming, and costly treatment [2, 3]. The DIPI technique represents a good alternative to other techniques in infertile women with patent fallopian tubes. Superovulation to increase the number of oocytes available for fertilization and DIPI to increase the concentration of motile spermatozoa and their proximity to the oocytes have been used in infertile couples to determine the efficacy of this combination of techniques. Described here is a case (unexplained infertility) of pregnancy resulting from DIPI during ovarian hyperstimulation cycles induced with gonadotropin-releasing hormone (GnRH) analogue.

## Case reports

The patient was a 28-year-old female, gravida 0, para 0, with regular menstrual cycles and with a 3-year history of infertility. She had been investigated extensively, with the results showing a normal body temperature chart, normal post-coital test, normal endometrial biopsy, normal hysterosalpingography and normal laparoscopy with bilateral patent tubes and no evidence of adhesions or endometriosis. The husband had a diagnosis of oligoasthenozoospermia. He was given kallidinogenase (300 IU/day) (Carnaculin; Sanwa Kagaku Kenkyusho Co. Ltd., Tokyo, Japan) for 5 months, and consequently, normal findings in semen analysis were seen. Subsequently, the patient underwent intrauterine insemination (IUI) unsuccessfully during three cycles induced with clomiphene and during five cycles with clomiphene and human menopausal gonadotropin (HMG) (Humegon; Organon, Cambridge, UK). Serum estradiol-17 $\beta$  (E2) concentrations and the number of HMG (150IU) ampules administered in IUI cycles with HMG reached a mean

value of  $374 \pm 48$  pg/ml and  $6.8 \pm 0.8$  ampules on the day of human chorionic gonadotropin (HCG) (HCG Mochida; Mochida, Tokyo, Japan) injection, respectively.

The patient then underwent DIPI using a long GnRH analogue and HMG protocol. Buserelin acetate (900  $\mu$ g/day) (Suprecur; Hoechst, Frankfurt, Germany) as a GnRH analogue was administered nasally beginning on day 23 of the menstrual cycle. Following pituitary desensitization with buserelin acetate, follicular stimulation was achieved with one ampule of HMG daily for 10 days. Follicular growth was monitored only by ultrasound using a vaginal probe, and 5000 IU of HCG were given when two follicles  $> 17$  mm (18x17x17 mm in the right and 18x19x17 mm in the left) in diameter were observed (other follicles  $\geq 10$  mm: 3 in the right ovary and 4 in the left). E2 and progesterone levels in serum reached 1695 pg/ml and 0.8 ng/ml on the day of HCG injection, respectively. Semen was prepared by the standard swim-up technique (HTF medium) and  $4.8 \times 10^6$  progressive motile spermatozoa were inseminated (fresh semen: 3 ml,  $55 \times 10^6$  spermatozoa/ml, 56% progressive motility, 70% normal forms; post swim-up:  $6 \times 10^6$  spermatozoa/ml, 92% progressive motility, 100% normal forms). Washed sperm sample (0.8 ml) was aspirated into a tuberculin syringe and injected using an 18-gauge needle into the pouch of Douglas through the posterior fornix of the vagina after aspiration of peritoneal fluid, 37 hours after HCG.

Eleven days after DIPI, moderate ovarian hyperstimulation syndrome (OHSS) [4] was observed and the patient was admitted. The right and left ovaries measured 4x7 cm and 6x9 cm in diameter respectively, and mild ascites was observed by ultrasound. The patient was treated with fluid and plasma infusions. The OHSS gradually improved and the patient was discharged 10 days later.

Twelve days after DIPI,  $\beta$ -HCG in serum was positive and the patient is currently in the third trimester of a normally proceeding twin pregnancy without further complications.

## Discussion

The aim of ovulation induction by gonadotropin is to increase the number of mature oocytes and consequently

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the chance of conception. It has been reported that a higher pregnancy rate could be obtained with cycles stimulated with HMG than with clomiphene citrate in IUI or DIPI [5].

In our case, several cycles of superovulation with HMG in IUI could not produce plural mature follicles. Therefore, the use of hormonal superovulation induced with GnRH analogue, successful in vitro fertilization and embryo transfer (IVG-ET) programs, is applicable to DIPI protocols in which increasing the number of potentially fertilizable oocytes is thought to be advantageous. Consequently, in the case described, plural mature follicles were obtained by means of this protocol.

The possibility of severe OHSS as a life-threatening complication [6, 7] should be kept in mind. The probability of occurrence of OHSS correlates well with the level of estradiol and the number of follicles on the day of HCG administration [8]. Therefore, in addition to the monitoring of follicular growth using ultrasonography, determinations of serum estradiol levels are useful to monitor the quality of the ovarian response and to avoid development of severe hyperstimulation [9].

Additionally, the high multiple birth rate is a consequence of the polyfollicular recruitment. In DIPI with superovulation, the highest possibilities of becoming pregnant and having a multiple pregnancy occur when the number of stimulated follicles has reached seven to eight [10].

In conclusion, for unsuccessful cases in regular superovulation, DIPI in ovarian hyperstimulation cycles induced with GnRH analogue should be tried before venturing into more costly and invasive programmes such as GIFT and IVF-ET. However, serious attention must be given to the possibility of OHSS and multiple pregnancy.

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