Pregnancy with 15 live fetuses and severe ovarian hyperstimulation syndrome after ovulation induction and intrauterine insemination

S.M. Abbas, A.A. Rouzi

Department of Obstetrics and Gynecology, King Abdulaziz University, Jeddah (Saudi Arabia)

Summary

The empirical use of ovulation induction and intrauterine insemination for male factor infertility, unexplained infertility, and anovulatory infertility can be associated with multiple gestation and ovarian hyperstimulation syndrome (OHSS). A 30-year-old lady was referred for fetal reduction of very high-order pregnancy. She became pregnant after ovulation induction and artificial insemination. The stimulation protocol included clomiphene citrate and fixed-dose gonadotropins. Triggering of ovulation was done with 5,000 units of human chorionic gonadotropins (hCG). Cycle monitoring was done with ultrasonography only. The patient was admitted to the hospital due to severe OHSS. Physical examination revealed that the uterus size was equivalent to 28 weeks gestation. Transvaginal ultrasonography (TVUS) and pelvic magnetic resonance imaging (MRI) showed 15 intrauterine gestational sacs with viable eight-week fetuses and 7 cm x 4.5 cm fluid collection. Both ovaries were enlarged. The right ovary was 12 cm x 5 cm and the left ovary was 10 cm x 6.5 cm. The patient had a spontaneous miscarriage of the 15 fetuses.

Key words: Multiple gestation; OHSS; Ovulation induction.

Introduction

The aim of ovulation induction is to produce two to three mature follicles and ova for in vivo fertilization (IVF). Multiple gestation and ovarian hyperstimulation syndrome (OHSS) are known complications of ovulation induction with exogenous gonadotropins and intrauterine insemination. Severe OHSS is a life-threatening condition which results in hospitalization in 1.9% [1]. Severe OHSS can cause strokes, kidney failure, heart attack, and even death, although these consequences are extremely uncommon with adequate treatment. Guidelines and strategies for prevention of high-order pregnancy and OHSS after assisted reproductive technologies (ART) are well-established and include daily monitoring of estradiol level and transvaginal ultrasonography (TVUS) [2]. Inadequate cycle monitoring can result in medical catastrophic situations [3]. The aim of this case report was to document a case of very high-order multiple gestation and severe OHSS after ovulation induction and intrauterine insemination.

Case Report

A 30-year-old lady in her third pregnancy was referred for fetal reduction of very high-order pregnancy. She became pregnant after ovulation induction and artificial insemination for male factor infertility. The stimulation protocol included clomiphene citrate 100 mg orally from the second day of her menstrual cycle for five days and human menopausal gonadotropins (hMG) 150 IU daily from the third day of her period for ten days. Triggering of ovulation was done with 5,000 units of human chorionic gonadotropins (hCG). Cycle monitoring was done with ultrasonography only. She was admitted to the hospital for 16 days due to severe OHSS with right pleural effusion four weeks prior to the referral. She had two previous full-term normal deliveries. Physical examination revealed that the uterus size was equivalent to 28 weeks gestation. TVUS and pelvic magnetic resonance imaging (MRI) showed 15 intrauterine gestational sacs with viable eight-week fetuses (Figures 1 and 2) and 7 cm x 4.5 cm fluid collection (Figure 3). Both ovaries were enlarged (Figure 2). The right ovary was 12 cm x 5 cm and the left ovary was 10 cm x 6.5 cm. No selective reduction was done. She had a spontaneous miscarriage of the 15 fetuses.

Discussion

Infertility is estimated to affect 10% to 15% of couples. The incidence of multiple pregnancy has increased dramatically in the last two decades due to new technologies and advances in reproductive medicine that overcome infertility. The rate of spontaneous twin pregnancy has been estimated to range from 1% to 1.35% and that of a triplet pregnancy from 0.01% to 0.017%. The incidence of multiple gestations is more than ten to 20 times higher with ovulation induction and intrauterine insemination, ranging from 7.5% to 29% per couple [4]. Treatment of male factor infertility with ovulation induction and intrauterine insemination is empirical. It is thought to work by increasing the number of ovarian follicles and depositing the good quality selected sperms in the uterine cavity. The two major complications of ovulation induction and intrauterine insemination are multiple pregnancy especially high-order pregnancy (triplets and more) and OHSS. The maternal risks of multiple pregnancy are well-documented. These include hypertension, preterm

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Fig. 1

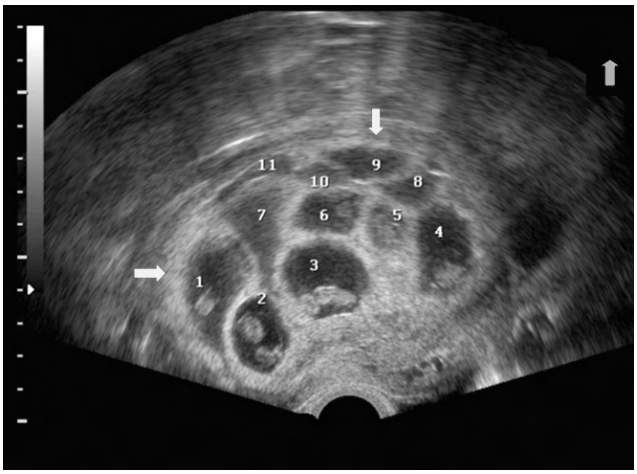

Fig. 2

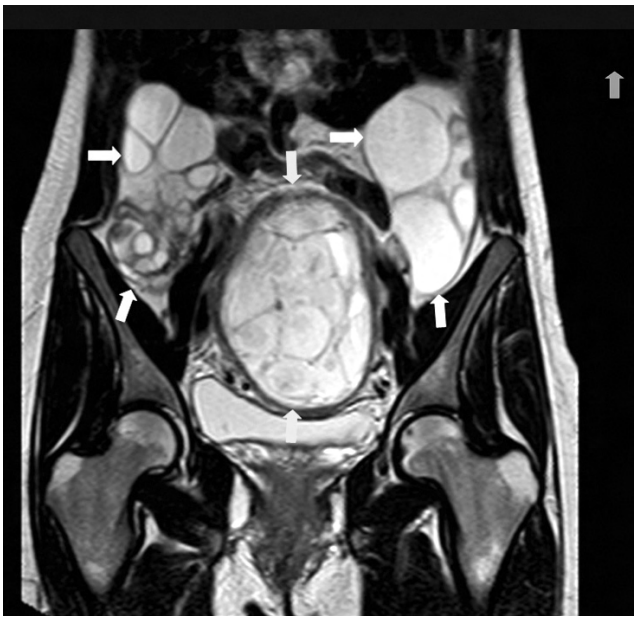

Fig. 3

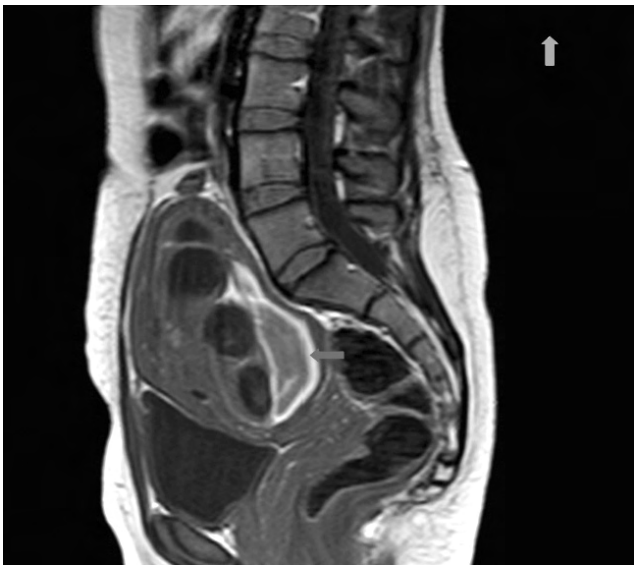

Figure 1. — TVUS image demonstrating multiple (11 out of 15) gestational sacs (as numbered) in the selected image.

Figure 2. — T2 weighted coronal image showing A: Multiple gestational sacs appearing with high signal intensity (fluid intensity) and focal areas of low signal intensity within representing the fetal poles; B: Enlarged ovaries (hyperstimulation syndrome).

Figure 3. — T1 sagittal image showing an intrauterine near soft tissue signal intensity along the posterior aspect representing a hemorrhage.

labor and delivery, postpartum hemorrhage, anemia, and emotional distress. There are many ovulation induction protocols. Clomiphene citrate alone, exogenous gonadotropins alone, or clomiphene citrate in combination with exogenous gonadotropins are commonly used for ovulation induction and intrauterine insemination. The risks of multiple pregnancy and OHSS increase with the use of exogenous gonadotropins. Maternal age < 32 years, high gonadotropins starting dose, longer days of stimulation, and number of follicles are important risk factors that increase the occurrence of multiple gestation. In series of more than 4,000 cycles or more than 1,800 pregnancies, twin pregnancies ranged from 15% to 20% and high-order pregnancies from 5.7% to 8.8% when the initial dose of gonadotropins was 150 IU or greater. In contrast, in series of more than 500 cycles using minimal stimulation initial doses of 37.5 - 75 IU of gonadotropins, twin implantations ranged from 6% to 15% and high-order pregnancies from 0 to 1.3% [5]. Similarly, with 150 IU of gonadotropins, high-order pregnancies increased from 4% when stimulation was less than nine days to 14% when stimulation lasted more than 12 days. Strategies to prevent multiple gestation include the use of mild stimulation protocol, the use of low-starting dose of gonadotropins, daily monitoring of ovarian response, and cancelation of the cycle when there are more than three follicles 15 mm or more according to the American College of Obstetrics and Gynecology [6]. The sequential use of clomiphene citrate followed by gonadotropins from cycle days seven to nine is thought to be “mild stimulation protocol” which would reduce the incidence of multiple gestation when compared to gonadotropins-only protocol. However, recent studies suggest that multiple gestation and cancellation rates are similar to gonadotropins-only protocol [5]. The stimulation protocol used in the current report is different than the typical sequential protocol of clomiphene citrate and gonadotropins. Fixed dose of gonadotropins were given daily from the third day of the menstrual cycle for ten days.

All ovarian stimulation protocols result in some degree of hyperstimulation, usually with no adverse conse-

quences to the patient. In contrast, OHSS is an iatrogenic complication of ovulation induction and is characterized by ovarian enlargement, third spacing of fluid, hemoconcentration, and even systemic organ function impairment with the need for hospitalization, sometimes in intensive care units. Severe OHSS can be a life-threatening situation for a young previously healthy woman. The best strategy to deal with OHSS is prevention. Women at risk of OHSS include young age, a history of elevated response to gonadotropins, previous OHSS, polycystic ovary syndrome, high estradiol level, development of high number of follicles, and exposure to hCG. Complete prevention of OHSS is still not possible. Early identification of potential risk factors and careful daily monitoring with estradiol and TVUS can result in significant reduction in the incidence of OHSS [2]. In addition, coasting of the cycle, reduced dose of hCG, triggering of final oocyte maturation with gonadotpins releasing hormone agonist (instead of hCG) and cancellation of the cycle can be helpful to prevent OHSS. In the Western World, treatment is monitored by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve patient satisfaction [7]. However, in the developing world, due to many factors including limited resources and inadequate cycle monitoring can result in medical catastrophic situations as illustrated in the current case and a published case series [3].

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Address reprint requests to:
A. ROUZI, M.D.
Department of Obstetrics and Gynecology
King Abdulaziz University
P.O. Box 80215
Jeddah, 21589 (Saudi Arabia)
e-mail: aarouzi@gmail.com