Article

Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles

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Abstract

A retrospective study was conducted in a private infertility centre to evaluate the rate of complications in a large oocyte donation programme. A total of 4052 oocyte retrievals were performed between January 2001 and October 2007. Altogether, 1238 cycles (30.6%) were stimulated with the use of gonadotrophin-releasing hormone (GnRH) agonists and in 2814 cycles (69.4%) the GnRH antagonist protocol was used. The GnRH antagonist treated cycles were triggered with human chorionic gonadotrophin (HCG) or a GnRH agonist in 1295 and 1519 cycles, respectively. Complications related to oocyte retrieval occurred in 17 patients (0.42%) (intra-abdominal bleeding: $n = 14$, severe pain: $n = 2$, ovarian torsion: $n = 1$). Fourteen of these were hospitalized (0.35%) and six donors (0.15%) required surgical intervention. Pelvic infections, injury to pelvic structures or anaesthesiological complications were not observed in this series. Moderate/severe ovarian hyperstimulation syndrome (OHSS) occurred in 22 donors; 11 required hospital admission and 11 were managed on an outpatient basis. All cases were related to HCG triggering (0.87%). Serious complications related to oocyte retrieval occurred at a low rate in healthy young donors. The risk of OHSS can be substantially reduced by specific stimulation protocols, which include GnRH agonist triggering. Prospective oocyte donors should be adequately counselled about the risks related to egg donation.

Keywords: *OHSS, oocyte donation, transvaginal ultrasound-guided oocyte retrieval*

Introduction

Since the advent and worldwide spread of oocyte donation (Lutjen *et al.*, 1984), the indications for this particular treatment option grow continually, with a concomitant increased demand for egg donors. The regulation of egg donation and the availability of egg donors vary considerably between countries. In some, there is a complete prohibition of gamete donation, others allow egg sharing in IVF patients, while others allow the recruitment of altruistic or paid voluntary donors (Sauer and Kavic, 2006). In any case, special effort should be made to minimize the burden of treatment and potential treatment risks for oocyte donors.

Since the description of transvaginal ultrasound-guided oocyte retrieval (Wikland *et al.*, 1985), several observational studies have evaluated the rate of complications related to this procedure (Bennet *et al.*, 1993; Dicker *et al.*, 1993; Tureck *et al.*, 1993; Roest *et al.*, 1996; Govaerts *et al.*, 1998). These studies have shown that the procedure can be considered as safe, with rates of serious complications varying between 0.02 and 0.3% for intra-abdominal bleeding, 0.01 and 0.6% for pelvic infection and 0.08 and 0.13% for ovarian torsion. Cases of bowel, ureter and pelvic vessel injuries have been described as case reports (Van Hoorde *et al.*, 1992; Bennet *et al.*, 1993; Akman *et al.*, 1995; Roest *et al.*, 1996; Coroleu *et al.*, 1997; Miller *et al.*, 2001; Fiori *et al.*, 2006, Ludwig *et al.*, 2006).

Information is very scarce regarding complication rates in oocyte donors. Sauer (2001), in a retrospective series of 1000

cases, observed seven serious complications, including severe ovarian hyperstimulation syndrome (OHSS), adverse reaction to anaesthetics, intra-abdominal bleeding and bladder atony with haematuria. It is universally acknowledged that despite their young age and potentially high ovarian response, donors have low probabilities of developing OHSS due to the absence of subsequent pregnancy (Sauer *et al.*, 1996). Nevertheless cases involving oocyte donors with severe early-onset OHSS have been reported in the literature (Halme *et al.*, 1995; Sauer, 2000).

With the advent and increasing use of gonadotrophin-releasing hormone (GnRH) antagonist protocols the substitution of human chorionic gonadotrophin (HCG) with a GnRH agonist as a triggering agent of final oocyte maturation became possible. Uncontrolled, observational trials described a beneficial effect, virtually eliminating OHSS in high-risk IVF patients (Itskovitz-Eldor *et al.*, 2000; Kol and Muchtar, 2005). To date, only a few small-scale studies (Acevedo *et al.*, 2006; Shapiro *et al.*, 2007) have evaluated the effect of GnRH agonist triggering in oocyte donation cycles. These were, however, insufficiently powered to detect any difference in clinically significant OHSS. The concept of GnRH antagonist stimulation protocol, combined with GnRH agonist triggering, is of great interest in this patient group (Griesinger *et al.*, 2006), as it represents a safe OHSS-free treatment option for the egg donor and a favourable outcome for the recipient.

In recent years, the clinical practice of oocyte donation programme has gradually changed in favour of the use of the GnRH antagonist protocol for donor stimulation (Bodri *et al.*, 2006), with a concomitant ever increasing proportion of GnRH agonist-triggered cycles. The aim of the present retrospective study was to evaluate the rate of complications related to oocyte retrieval and ovarian stimulation in a large cohort of oocyte donation cycles in order to be able to give precise information concerning risks related to egg donation to prospective oocyte donors.

Materials and methods

Oocyte donors

All consecutive oocyte donation cycles that were performed in a private fertility centre in which donors reached oocyte retrieval were analysed retrospectively. The study period was between January 2001 and October 2007. Data were obtained from an exhaustive review of all medical charts related to oocyte donors. In cases of hospitalization, a medical report was obtained from the centre where the patient was treated. Oocyte donation was performed according to the Spanish Act on Assisted Reproduction. Donation was anonymous and altruistic, and donors were required to be between 18 and 35 years of age. A conventional clinical (including coagulation screening tests) and psychological workup was performed, including karyotype. Although it was not the primary aim of the study, a control group was created by taking into account all IVF (not oocyte donor) cycles reaching oocyte retrieval performed during the same period.

Ovarian stimulation

Ovarian stimulation protocols were described previously (Bodri *et al.*, 2006). In the first half of the study period (2001–2003), donor stimulation was performed with the use of GnRH agonists predominantly with the short 'flare-up' protocol. In a few cases, the 'classical' luteal phase long agonist protocol was also used. From the second half of the study period (2004–2007) the flexible GnRH antagonist protocol was used increasingly. In the GnRH agonist protocols, triggering was performed with 250 µg recombinant human chorionic gonadotrophin (rHCG) (Ovitrelle; Serono, Madrid, Spain). In the GnRH antagonist protocols, the triggering agent was chosen by the physician, taking into account the total number of follicles and/or the final serum oestradiol concentration, either recombinant HCG or the GnRH agonist in the form of 0.2 mg of triptorelin s.c. (Decapeptyl; Ipsen Pharma, Barcelona, Spain).

Oocyte retrieval

A single-dose of 1 g of azythromycine was administered as a prophylactic antibiotic on the evening before the intervention (Zitromax; Pfizer, Madrid, Spain). Oocyte retrieval was performed with the transvaginal ultrasound-guided approach using a 17G ovum-aspiration needle (Cook Ireland Ltd, Limerick, Ireland). The ultrasound probe was thoroughly disinfected before and after use and covered with a sterile plastic sheet. The vagina was disinfected with chlorhexidine and thereafter abundantly rinsed with isotonic saline solution. The patient was covered with sterile surgical sheets and the gynaecologist performing the procedure wore sterile surgical gloves. The intervention was performed under general anaesthesia by an anaesthesiologist using intravenous alfentanyl (Limifen; Janssen-Cilag, Barcelona, Spain) and propofol (Recofol; Schering, Madrid, Spain) as well as assisted mask ventilation with oxygen and an inhalatory anaesthetic (Sevorane; Abbot, Madrid, Spain). At the end of the procedure, the vagina was thoroughly examined with a speculum and if necessary local compression was applied to allow haemostasis. Donors were observed in a post-operative recovery unit for 2 h following the procedure, and were systematically contacted by telephone in the evening following oocyte retrieval. In the case of acute complications, donors were admitted to a tertiary university-affiliated centre.

Donor follow-up and management

After oocyte retrieval, all donors were informed about the possible symptoms of intra-abdominal bleeding or infection as well as about OHSS and its preventive measures. They were also counselled to avoid sexual intercourse until their next menstrual period. From the day of the oocyte retrieval, systematic follow-up was performed by telephone, and if necessary, donors were managed on an outpatient basis until 2 weeks after the procedure. Every donor was encouraged to present for check-up if experiencing any symptoms. On consultation, physical examination, vaginal and abdominal ultrasound scan and blood analysis were performed. In the case of OHSS, the outpatient management comprised bed rest, fluid balance monitoring and symptomatic therapy to relieve pain and discomfort. OHSS was classified according

to criteria described by Navot *et al*. (1992). Donors diagnosed with mild/moderate OHSS were followed up every 48 h until a complete resolution of the syndrome had been achieved. Donors were hospitalized where there was a high risk of developing severe OHSS or if there was no clinical improvement during outpatient management. Inpatient treatment was conducted according to a previously published conservative medical approach (Balasch *et al*., 1996).

Outcome measures

Primary outcome measures were the incidence of serious complications (intra-abdominal bleeding, ovarian torsion, infection, injury or severe pain) related to oocyte retrieval requiring hospitalization or outpatient management. The secondary outcome measure was the incidence of moderate/severe ovarian hyperstimulation syndrome (OHSS) in oocyte donors requiring hospitalization or outpatient management.

Statistical analysis

Nominal variables were analysed by the chi-squared test. $P < 0.05$ was considered statistically significant.

Results

A total of 4052 stimulation cycles that reached oocyte retrieval performed on 1917 donors was analysed retrospectively. A total of 1238 cycles (30.6%) was stimulated with the GnRH agonist protocol, whereas in 2814 cycles (69.4%) the GnRH antagonist protocol was used. In the GnRH antagonist treated cycles the triggering agent was HCG in 1295 cycles, whereas in 1519 cycles a GnRH agonist was used to induce final oocyte maturation. Trends in different stimulation protocols and triggering agents used during the study period are shown in **Figure 1**.

Fourteen patients (0.35%) were hospitalized due to complications related to oocyte retrieval; the diagnoses and the received treatments are summarized in **Table 1**. The mean duration of hospital stay was 2.6 days (range: 0.5–7 days). Intra-abdominal bleeding was diagnosed in a total of 14 donors (0.35%); five of them required surgery (0.12%), four patients by laparoscopy and one patient by laparotomy. One patient who had surgery received a transfusion. In the remaining nine donors (six of them hospitalized and three followed with outpatient management alone), the bleeding showed to be self-limiting during the observation period and no intervention was necessary. One case of unilateral ovarian torsion (0.024%) occurred and the patient was successfully operated on by laparoscopy keeping her ovary intact. Two patients were hospitalized for pain treatment following oocyte retrieval. No cases of pelvic infection or injury of pelvic anatomical structures were observed in this series. No anaesthesiological complication occurred in the study group.

Early-onset moderate/severe OHSS was diagnosed in 22 donors during the first week following oocyte retrieval. OHSS occurred only in cases where rHCG was used as a triggering agent (0.87%). Eight donors were stimulated with the GnRH agonist, while 14 with the GnRH antagonist protocol. Ultrasound and/or clinical evidence of ascites were found in all patients. Haemoconcentration (Hct ≥ 45) was found in eight patients, whereas elevated liver enzymes were found in nine cases. Eleven patients required hospitalization; six of them were severe OHSS cases. The mean duration of hospital stay was 5.2 days (range: 1–9 days). Ascites puncture was performed by culdocentesis in one patient. All donors recovered completely within 2 weeks of oocyte retrieval, with outpatient management alone or after hospitalization. The incidence of moderate/severe OHSS according to the stimulation protocol and triggering agent used is summarized in **Table 2**.

In the control group, a total of 1047 oocyte retrievals were performed on 736 IVF patients (age range: 21–46 years). Intra-abdominal bleeding was diagnosed in two patients (0.27% of patients, 0.19% of cycles); one patient was operated on by laparoscopy and the other one remained in observation. Moderate/severe OHSS occurred in 15 patients (2.04% of patients, 1.43% of cycles), nine of whom were hospitalized. Eight of the above-mentioned cases were early-onset related to HCG triggering, whereas the late-onset form related to embryonic implantation occurred in seven cases (**Table 3**).

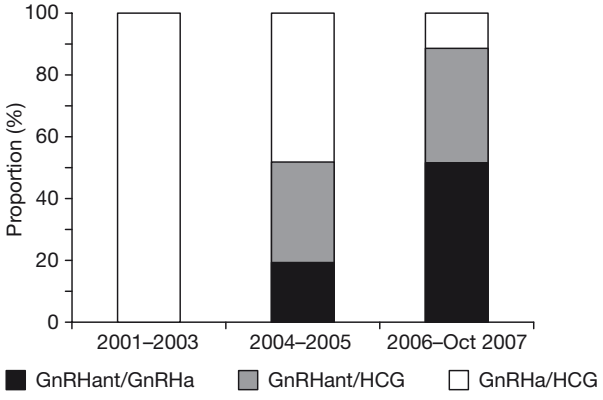

Figure 1. Trends in different stimulation protocols and triggering agents used during the study period. GnRHa = gonadotrophin-releasing hormone agonist; GnRHant = GnRH antagonist; HCG = human chorionic gonadotrophin.

Table 1. Description of donors hospitalized following oocyte retrieval.

Donor	*Number of retrieved oocytes*	*Diagnosis*	*Treatment*	*Hospital stay (days)*
1	18	Intra-abdominal bleeding	Laparoscopy	3
2	20	Intra-abdominal bleeding	Laparoscopy	3
3	23	Intra-abdominal bleeding	Laparoscopy	6
4	8	Intra-abdominal bleeding	Laparoscopy + transfusion	2
5	16	Intra-abdominal bleeding, acute abdomen	Laparotomy	5
6	19	Intra-abdominal bleeding	Observation	1
7	19	Intra-abdominal bleeding	Observation	1
8	5	Intra-abdominal bleeding	Observation	1
9	4	Intra-abdominal bleeding	Observation	2
10	23	Intra-abdominal bleeding	Observation	3
11	10	Intra-abdominal bleeding	Observation	7
12	30	Ovarian torsion	Laparoscopy	1.5
13	13	Pain	Observation	1
14	7	Pain	Observation	0.5

Table 2. The incidence of moderate/severe ovarian hyperstimulation syndrome (OHSS) according to the stimulation protocol and triggering agent used in donor oocyte cycles.

Stimulation protocol/triggering agent	*No. of cycles*	*Moderate/severe OHSS* (n)	*Incidence % (95% CI)*
GnRH agonist/HCG	1238	8	0.65[a] (0.33–1.27)
GnRH antagonist/HCG	1295	14	1.08[a] (0.64–1.80)
GnRH antagonist/GnRH agonist	1519	0	0 (0–0.25)

[a]Chi-squared test (not statistically significant).
CI = confidence interval; GnRH = gonadotrophin-releasing hormone; HCG = human chorionic gonadotrophin.

Table 3. Complications in the IVF control group (1047 cycles).

Type of complication	*No. of cases*	*Incidence % (95% CI)*
Intra-abdominal bleeding	2	0.19 (0.05–0.68)
Early-onset moderate/severe OHSS	8	0.76 (0.39–1.49)
Late-onset moderate/severe OHSS	7	0.66 (0.33–1.37)
Moderate/severe OHSS (all cases)	15	1.43 (0.87–2.34)

CI = confidence interval; OHSS = ovarian hyperstimulation syndrome.

Discussion

This retrospective study, performed on a large cohort of oocyte donor cycles, showed that a low rate of serious complications can be expected following oocyte retrieval. The most frequent complication was intra-abdominal bleeding, which in approximately in one-third of the cases required surgical intervention. No cases of pelvic infection or injury of anatomical structures were diagnosed in the study group. Moderate/severe OHSS also occurred at an overall low rate, as expected in oocyte donors. Moreover, its pathogenesis was directly related to the type of stimulation protocol used. The substitution of HCG with the GnRH agonist as a triggering agent virtually eliminated the risk of clinically significant OHSS.

Minor vaginal bleeding that stops spontaneously or after local compression can frequently occur following oocyte retrieval in up to 8.6% of cases (Bennett *et al*., 1993). It rarely requires other measures than local compression for <1 min, although exceptionally vaginal tamponade or suture is applied (Ludwig *et al*., 2006). On the other hand, intra-abdominal bleeding is a more serious complication that is usually caused by trauma of vessels of the ovarian capsule or bleeding from ruptured follicles. According to the estimation of Dessole *et al*. (2001), an average 230 ml blood loss can be considered normal during the first 24 h after non-complicated transvaginal oocyte retrieval. Retrospective studies observed a rate of intra-peritoneal bleeding or haemoperitoneum varying between 0.02 and 0.3% (Bergh and Lundkvist, 1992; Bennett *et al*., 1993; Dicker *et al*., 1993; Tureck *et al*., 1993; Govaerts *et al*., 1998), whereas no cases were observed in the prospective study of Ludwig *et al*. (2006). This complication was also described in case reports as a consequence of coagulation disorders such as essential thrombocythemia (El-Shawarby *et al*., 2004a,b) or factor XI deficiency (Battaglia *et al*., 2001). A case report by Moayeri *et al*. (2007) described a patient with von Willebrand disease initially undetected by routine coagulation screening tests who had recurrent haemorrhage after oocyte retrieval. The present study included cases not requiring surgical intervention (9 of 14 donors) due to the minor degree of intra-peritoneal blood loss managed by hospital observation or outpatient care alone.

Whereas in the literature the rate of pelvic infections following oocyte retrieval in IVF patients was reported to be between 0.01 and 0.6% (Dicker *et al*., 1993; Bennet *et al*., 1993; Tureck *et al*., 1993; Roest *et al*., 1996; Ludwig *et al*., 2006), in the study group no cases were observed. This can probably be explained at least in part by the absence of significant risk factors such as the history of pelvic inflammatory disease or the presence of hydrosalpinges and severe endometriosis among oocyte donors (Moini *et al*., 2005; El-Toukhy and Hanna, 2006). The benefit of preventive antibiotics seems to be controversial (El-Shawarby *et al*., 2004a,b), and in the current protocol they were given on an empirical basis.

Adnexal torsion is a very rare but serious complication related to ovarian stimulation. The presence of enlarged and at the same time mobile ovaries is recognized as a predisposing factor. Retrospective series report its incidence between 0.08 and 0.13% (Roest *et al*., 1996; Govaerts *et al*., 1998), in some cases involving the loss of the patient's ovary.

Trauma to pelvic structures (bladder, ureter, bowel, large vessels, nerves) caused by the ovum aspiration needle is a potentially severe complication of ultrasound-guided oocyte retrieval. To date, only case reports have been published in the literature. Cases of perforated appendix have been described by several authors (Van Hoorde *et al*., 1992; Akman *et al*., 1995; Roest *et al*., 1996). Several cases of ureter injury have been reported (Coroleu *et al*., 1997; Miller *et al*., 2001; Fiori *et al*., 2006; Ludwig *et al*., 2006), which often can represent a diagnostic challenge. The much-feared case of a large vessel injury was described in the series of Bennet *et al*. (1993), with favourable resolution by conservative management. In comparison, a massive retroperitoneal haematoma following injury of a sacral vein and requiring surgical intervention was described by Azem *et al*. (2000).

To date, the incidence of OHSS in the context of oocyte donation has only been addressed by a few studies. Sauer *et al*. (1996) reported a 1.5% incidence of severe OHSS in a series of 400 long agonist donor cycles. Despite high peak oestradiol concentrations, no severe complications occurred and hospitalization was not required. This relatively favourable course is due to the absence of a subsequent pregnancy; compared with IVF patients, donors are exposed only to HCG-induced early OHSS. Similarly, Morris *et al*. (1995), in a series of 139 high-risk patients with high oestradiol concentration and oocyte yield, concluded an absence of severe OHSS in the donor group (72 patients) compared with around 10% (6/61) in the IVF patient group. In comparison, in IVF patients the incidence of OHSS is generally estimated to be 3–6% for the moderate and 0.1–2% for the severe form, but there is considerable variation according to different studies and due to the different classifications used (Delvigne and Rozenberg, 2002).

With the advent and the increasing use of GnRH antagonist protocols, considerable interest has emerged in GnRH triggering. Uncontrolled, observational trials described a beneficial effect, virtually eliminating OHSS in high-risk patients (Itskovitz-Eldor, 2000; Kol and Muchtar, 2005). This fact was due to a complete, quick and irreversible luteolysis that followed the flare-up effect of the GnRH agonist (Kol, 2004). To date, only small-scale studies have evaluated the outcome of GnRH agonist triggering in oocyte donation cycles. Due to their sample size, they were insufficiently powered to detect any difference in clinically significant OHSS. Acevedo *et al*. (2006), in a prospective randomized trial with 30 donors in each treatment arm, detected a significant difference in favour of the agonist group (5/30 versus 0/30). Nevertheless, all of their OHSS cases were of a mild degree. Shapiro *et al*. (2007), in a retrospective study of similar size, found only one case of OHSS in the HCG group requiring culdocentesis.

This retrospective series showed a clear advantage of GnRH agonist triggering with no cases of moderate/severe OHSS observed at all, as compared with donors treated with the HCG-triggered stimulation protocols. Moreover, even in the HCG-triggered group the rate of OHSS remained relatively low (0.87%). Interestingly, although it was not the aim of the present study, a trend towards a higher rate of OHSS was observed with the use of GnRH antagonists as compared with GnRH agonists (although this was not statistically significant). Published meta-analyses (Kolibianakis *et al*., 2006; Al-Inany *et al*., 2007) do not support the above finding; however, one must take into

account the retrospective nature of the data in comparison with those obtained from randomized clinical trials.

One of the main limitations of the present study is related to its retrospective nature, which has an inherent possibility for bias. However, due to strict donor follow-up and to thorough checking of all medical records during data retrieval, all clinically relevant complications related to donor cycles should have been registered.

In conclusion, the findings of this retrospective study from a cohort, which, as far as is known, is the largest published to date regarding oocyte donor cycles, confirm that egg donation is a safe procedure with a low rate of serious complications related to oocyte retrieval. The short-term risks of ovarian stimulation can be further reduced or even completely eliminated using innovative stimulation protocols that are specifically tailored for oocyte donors. Nonetheless, prospective oocyte donors should be thoroughly informed about existing short-term as well as potential long-term risks of the procedure.

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