Risk and Complications Associated with Egg Donation

16

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Key Points

- The overall rate of complications experienced by egg donors appears to be less than 1 % and is remarkably consistent between studies conducted in different regions of the world and with different clinical practices.
- The low complication rate in egg donors could be diminished even further by the systematic implementation of protocols that use GnRH agonists for the induction of final oocyte maturation.
- An average of 230-mL blood loss should be considered normal during the first 24 h after an uncomplicated transvaginal oocyte retrieval.
- Primary patient-related risk factors for complications include young age, previous history of OHSS, PCOS, and exaggerated markers of high ovarian reserve such as high antral follicle count or elevated levels of AMH.

Short-Term Complications of Oocyte Donation

Oocyte donation has been practiced for more than two decades and currently has wide indications. This has led to an increased demand and a continuous growth of oocyte donation cycles worldwide [1]. Although serious short-term complications are expected to occur at a relatively low rate, it is universally recognized that ovarian stimulation and oocyte retrieval might involve significant inconvenience and discomfort, as well as risk of injury to the donor.

The short-term risk complications have a defined timeline which helps in their correct differential diagnosis. Significant intra-abdominal bleeding is detected during the first 24 h after oocyte retrieval and prompts close observation or surgical exploration. Smaller-scale, self-limiting intraperitoneal bleeding causes persistent lower abdominal pain during the first few days and might be detected with transvaginal ultrasound scanning. Other potential complications such as adnexal torsion or pelvic infections rarely occur during the first week after oocyte retrieval. In contrast, the symptoms of an early-onset ovarian hyperstimulation syndrome (OHSS) usually appear 3–9 days after hCG administration and can persist up to 10–12 days afterward. Despite their young age and potentially high ovarian response, donors appear to have lower probabilities of developing OHSS due to the absence of subsequent pregnancy. Nevertheless, cases involving oocyte donors with severe early-onset OHSS have been reported in the literature [2].

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Table 16.1 Short-term major complication rates in oocyte donor series

Author, year	Oocyte retrievals, *n*	OR-related complications, *n* (%)	Moderate/severe OHSS, *n* (%)	Total, *n* (%)
Sauer (2001) [2]	1,000	4 (0.4)	3 (0.3)	7 (0.7)
Bodri et al. (2008) [4]	4,052	17 (0.42)	22 (0.54)	39 (0.96)
Maxwell et al. (2008) [5]	886	5 (0.56)	1 (1.1)	6 (0.7)
Sahuquillo et al. (2011) [3]	972	3 (0.31)	–	3 (0.31)
All studies	6,910	29 (0.42)	26 (0.38)	55 (0.80)

Overall rates of short-term, serious complications reported in oocyte donation series published during the last decade are presented in Table 16.1. The four available retrospective studies published to date reported a total of almost 7,000 treatment cycles [2–5]. The overall rate of complications is less than 1 % and is remarkably consistent between studies which were conducted in different regions of the world (USA and Europe) with different clinical practices. Approximately half of these short-term complications (at a total rate of 0.42 %) were related to the oocyte retrieval procedure. This type of complication might be reduced by technological advances (such as changes in ovum-aspiration needle design) improving the overall safety of transvaginal ultrasound-guided oocyte retrieval [6].

The other half of short-term complications were OHSS-related (at at total rate of 0.38 %) which in turn can be directly influenced by each center's ovarian stimulation policy. Convincing evidence shows that in any oocyte donation program, OHSS rates are negatively related to the proportion of GnRH antagonist stimulated/GnRH agonist triggered cycles used [4]. This implies that the overall expected <1 % short-term complication rate could be at least diminished by a half (to the level of the residual oocyte retrieval risk) by the introduction and systematic implementation of protocols which use GnRH agonists for the induction of final oocyte maturation. From a good clinical practice viewpoint, the fact that there is a stimulation protocol which can significantly increase the safety and well-being of oocyte donors is of great importance. The rate of minor, short-term disturbances experienced by oocyte donors were evaluated in only two of the above-mentioned studies varied between 8.5 and 12.5 % [3, 5].

Complications Related to Oocyte Retrieval

Since the description of transvaginal ultrasound-guided oocyte retrieval, several observational studies conducted in non-donor IVF patients have evaluated the rate of complications related to this procedure. 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 were described as case reports [7–10].

Intra-Abdominal Bleeding

Minor vaginal bleeding that stops spontaneously or after local compression frequently can occur following oocyte retrieval in up to 8.6 % of the cases. It rarely requires other measures than local compression for <1 min; exceptionally vaginal tamponade or suture is applied [7]. On the other hand, intra-abdominal bleeding is a more serious complication which is usually caused by trauma of vessels of the ovarian capsule or bleeding from ruptured follicles. According to the estimation of Dessole et al., an average 230-mL blood loss can be considered normal during the first 24 h after noncomplicated transvaginal oocyte retrieval [11]. Retrospective, non-donor IVF patient series observed a rate of intraperitoneal bleeding or hemoperitoneum varying between 0.02 and 0.3 %, whereas no cases were observed in the prospective study of Ludwig et al. [7]. This complication was also described in case reports as a

consequence of coagulation disorders such as essential thrombocythemia [12] or factor XI deficiency [13]. The case report of Moayeri et al. [14]. described a patient with von Willebrand disease initially undetected by routine coagulation screening tests who presented a recurrent hemorrhage after oocyte retrieval. In oocyte donation series, intra-abdominal bleeding was one of the main oocyte retrieval-related complications at a rate of 0.1–0.35 % [2, 4].

Pelvic Infection

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 %, in existing oocyte donation series no pelvic infection was reported. This can probably be explained at least in part by the absence of important risk factors such as the history of pelvic inflammatory disease or hydrosalpinges and severe endometriosis among oocyte donors [15, 16].

Adnexal Torsion

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, non-donor IVF patient series report its incidence between 0.08 and 0.13 % in some cases involving the loss of the patient's ovary. In oocyte donor series, there are three reported cases series yielding a comparable low incidence of 0.02–0.3 % [4, 5, 17].

Other Rare Complications

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 are published in the literature in non-donor IVF patients. Cases of perforated appendicitis were described by several authors. Several cases of ureter injury had been reported which often can represent a diagnostic challenge [7, 9, 10]. The much feared case of a large vessel injury was described in only one study with favourable resolution by conservative management. In comparison, a massive retroperitoneal hematoma following injury of a sacral vein and requiring surgical intervention was described by Azem et al. [18].

Anesthetic Complications

The rate of complications related to anesthesia in oocyte donors is low; a single case (0.1 %) of an adverse reaction to anesthetics was reported in the series of Sauer [2]. This might be explained by the fact that oocyte donors are usually young and healthy without any significant anesthesiological risk factors and are also thoroughly screened during their selection procedure.

Prevention and Management of Oocyte Retrieval-Related Complications

As a prerequisite for entering an oocyte donation program, a comprehensive donor screening and evaluation are recommended which apart from the exclusion of any infection or genetic risk also should include a complete screening for bleeding disorders. Additional tests might be needed in case of previous hemorrhagic complications. In order to reduce the risk of intra-abdominal bleeding during oocyte retrieval, an atraumatic technique is mandatory (avoiding repeated punctures of the vaginal wall, ovarian capsule, and follicles) [19]. A recent randomized clinical trial conducted in non-donor IVF patients evaluated the effect of reduced-size needle tip (17–20 G) on the overall pain experience after oocyte retrieval [6]. Although the degree of intra-abdominal bleeding was not evaluated, the authors have found significantly less vaginal bleeding, and patients also had significantly less pain. The risk of a pelvic infection following oocyte retrieval is low in oocyte donors, but it can be further reduced by

systematic screening and treatment of risk factors such as hydrosalpinges or undetected lower genital tract infections. The benefit of preventive antibiotics seems to be controversial, but they can be prescribed on an empirical basis after taking into account the potential side effects and the risk of an allergic reaction [16].

The postoperative observation following oocyte retrieval should be long enough (at least 2 h) to detect early alarm signs of short-term complications. Unstable blood pressure, tachycardia, or peritoneal irritation might be signs of significant intra-abdominal bleeding. Repeated transvaginal ultrasound scanning and serial hematocrit determinations are useful tools for confirming the suspicion. On the other hand, insufficient analgesia after oocyte retrieval might also cause similar symptoms such as hypotension, syncope, vagal reaction, nausea, and vomiting. After discharge from the unit, the ability to follow-up and access to a 24-h medical center for observation (in some cases for therapy of persistent severe pain) or eventual surgical intervention should be readily available. Significant intra-abdominal hemorrhage prompts a surgical—usually laparoscopic—intervention, and in almost all cases, conservative management is possible with no long-term consequences for the donor's health. In some cases, however, blood transfusion might be required [4]. In contrast, smaller, self-limiting intraperitoneal bleeding usually only needs observation during the first 24 h and outpatient follow-up afterward. For other less frequent complications (such as ovarian torsion or pelvic infection), the possibility of referring to a tertiary center, where diagnostic tools and surgical options are readily available, is recommended.

Ovarian Hyperstimulation Syndrome

Oocyte donors are only exposed to early-onset OHSS due to the absence of a subsequent pregnancy. This risk however should not be underestimated because donors are typically young women selected to have good ovarian reserve, and they frequently yield a large number of oocytes. It was estimated that donors who develop >20 follicles are exposed to a 15 % OHSS risk with the possibility of subsequent hospital admission [20]. The overall incidence of OHSS in the context of oocyte donation was addressed only by few studies. Sauer et al. reported a 1.5 % incidence of severe OHSS in a series of 400 long agonist donor cycles [21]. Despite high peak estradiol levels, no severe complications occurred, and hospitalization was not required. This relatively favorable course is due to the absence of a subsequent pregnancy, since unlike IVF patients, egg donors are exposed only to hCG-induced early OHSS. A more recent large randomized clinical trial which evaluated three different gonadotropin regimens (with a long agonist stimulation protocol and hCG trigger) including >1,000 oocyte donors reported a 5–7 % mild/moderate OHSS rate despite liberal cycle cancellation policy [22]. These studies highlight the fact that if effective preventive OHSS measures are not implemented, moderate/severe OHSS is expected to occur in oocyte donors in varying degrees depending on the type of stimulation protocol and triggering agent used.

Prevention of OHSS in Oocyte Donors

Several methods have been proposed for the prevention of clinically significant moderate/severe OHSS in non-donor patients undergoing ovarian stimulation for in vitro fertilization treatment (recently reviewed in Humaidan et al. 2010) [23]. Most of these can be easily applied in oocyte donors because any potential deleterious effect on the luteal phase can be disregarded. A didactical classification of different prevention strategies stratified by the time of their application (before stimulation, during stimulation, and after oocyte retrieval) is presented in Fig. 16.1 [24].

Identifying Risk Factors

Primary patient-related risk factors which are identifiable before starting ovarian stimulation include young age, previous history of high response or OHSS, PCOS characteristics, and

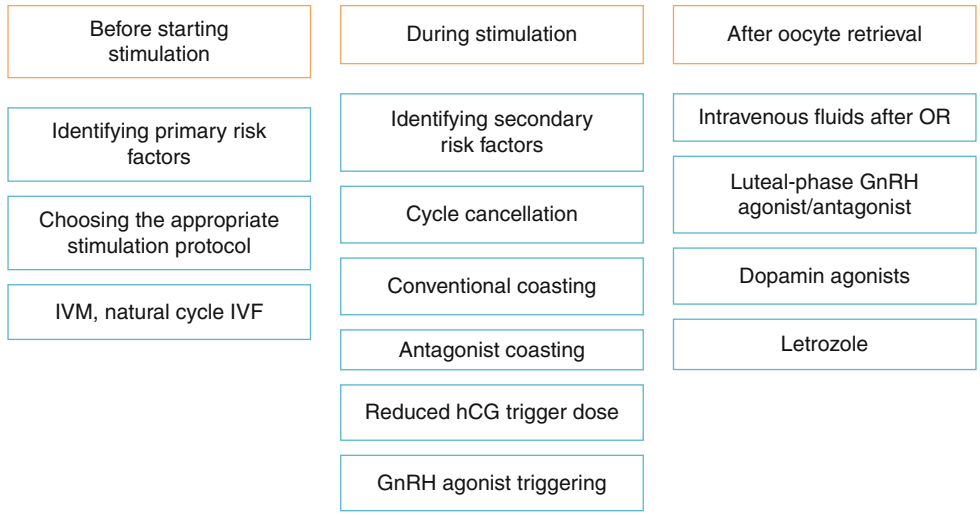

Fig. 16.1 OHSS prevention methods (Modified after Aboulghar (2009); Reprinted from Mohamed Aboulghar [24]. Copyright (2009), with permission from Elsevier)

markers of high ovarian reserve such as elevated antral follicle count (AFC) and serum anti-Mullerian hormone levels (AMH). In order to ensure high success rates, most oocyte donation programs have established donor age limits (usually <35 years old) although in some cases exceptions are made especially with "directed" known oocyte donation. The course of the donor's previous stimulation cycle is extremely useful but is not available for first-time donors. Oocyte donors with explicit PCOS syndrome are not ideal candidates, and their ovarian stimulation might be extremely difficult to manage with frequent cancellations for low response and longer duration of stimulation with an elevated OHSS risk. Therefore, it is questionable whether PCOS donors should be included at all in oocyte donation programs.

A recent large-scale European study evaluating >1,000 cycles stimulated with a long agonist protocol concluded that AFC was a useful, simple, and noninvasive tool for donor selection [25]. The authors have found that donors with AFC < 10 had a significantly higher cancellation rate for low response and fewer retrieved oocytes, but recipient pregnancy rates were not adversely affected. In contrast, cancellation rates for OHSS risk increased proportionally to higher AFC from 0.9 to 14 %. Similarly, AMH emerged as a promising serum marker of normal ovarian response or of elevated OHSS risk [26]. In the context of oocyte donation, recent studies have shown that AMH has a good correlation with the number of retrieved eggs and the need to decrease gonadotropin dose in order to avoid OHSS [27, 28]. A number of ovarian stimulation-related secondary risk factors exist such as follicular count on hCG triggering day, peak estradiol levels, and the number of retrieved oocytes, but they are of limited predictive value [29]. This is especially true for GnRH antagonist-based protocols where it was shown that compared to the follicular count on the day of hCG trigger, the peak estradiol level is less reliable at identifying OHSS-risk patients [30].

Personalizing Oocyte Donors' Stimulation Protocols

The choice of the most appropriate donor stimulation protocol is of paramount importance not only for optimizing ovarian response and to ensure high recipient success rates but also for establishing safe and simple stimulation for oocyte donors.

By extension from protocols used in non-donor IVF patients over many years, the classical long agonist regimen of stimulation was successfully applied to oocyte donors. It has offered the advantage of easy cycle programming which was

Table 16.2 Advantages and drawbacks of different donor stimulation protocols

Protocol type/triggering agent	Advantages	Drawbacks
Long agonist/hCG	Depot agonist	*OHSS risk*
		Longer duration
		Side effects
Short agonist/hCG	Less gonadotropin requirement (flare-up)	*OHSS risk*
GnRH antagonist/GnRH agonist	*No OHSS*	Higher cost
	Shorter duration	
	Depot antagonist	
No GnRH analogue or extended CC/GnRH agonist	*No OHSS*	LH surge?
	Shorter duration	Oocyte quality?
	Less expensive	

particularly important for donor-recipient synchronization [1]. Depot GnRH agonist preparations were also successfully used with this protocol offering the possibility of reducing the number of injections administered to the donor [31]. Although the short GnRH agonist protocol was found to be suboptimal in non-donor IVF patients, it has yielded good outcome when applied to oocyte donors [32, 33]. It has the advantage of shorter duration and of reducing the overall gonadotropin requirement due to the agonist's flare-up effect. On the other hand, it requires obligatory hCG triggering which carries an inherent OHSS risk [4]. Recently, a GnRH analogue-free stimulation protocol using extended follicular-phase clomiphene citrate (CC) administration was evaluated in a pilot study [34]. This innovative protocol takes advantage of the CC's ability of suppressing premature LH surges. Its main advantage lies in its cost-effectiveness and the possibility of oral administration, but recipient success rates still have to be evaluated in larger trial. The advantages and drawbacks of different donor stimulation protocols are summarized in Table 16.2.

Following their introduction into the clinical practice in the early 1990s, GnRH antagonists were also rapidly applied to stimulation of oocyte donors. Apart from the well-known advantages which contribute to donor commodity (shorter duration of stimulation and decreased gonadotropin consumption), the application of GnRH antagonists has also provided the possibility of substituting hCG with a GnRH agonist as the triggering agent for final oocyte maturation. A recent meta-analysis with a total sample of 1,024 donors summarized the findings of 8 randomized clinical trials which compared the use of different GnRH analogues for downregulation in oocyte donation [35]. The primary outcome measure was the rate of ongoing recipient pregnancies per randomized donor, and secondary outcome measures were the number of retrieved oocytes, the duration of stimulation, gonadotropin consumption, and OHSS incidence per randomized donor. As a main finding, this meta-analysis has found no significant difference in the number of retrieved oocytes (−0.6 COC, 95 % CI −2.26 to +1.07) or recipient ongoing pregnancy rates (RR 1.15, 95 % CI 0.97–1.36) between the two different protocols (Figs. 16.2 and 16.3). Moreover, with the GnRH antagonist protocol, stimulation duration was significantly lower (−0.9 days, 95 % CI −1.61 to −0.20), whereas gonadotropin consumption (−264 IU less, 95 % CI −682 to 154) and OHSS incidence (RR 0.62, 95 % CI 0.18–2.15) was also lower even if statistical significance was not reached due to sample size limitations. In practical terms, this means that currently available evidence suggests that in oocyte donors, GnRH antagonist-based protocols are as efficient as those based on GnRH agonists, but they are considerably safer (see section on "GnRH Agonist Triggering") and also have potential advantages for treatment simplification (possibility of using a single-dose GnRH antagonist protocol).

IVM/Natural Cycle IVF

In vitro maturation (IVM) has been recently evaluated in a prospective cohort study of 12 oocyte donors with PCOS or polycystic ovarian morphology [36]. After collecting an average 12.8 germinal-vesicle-stage oocytes per donor from

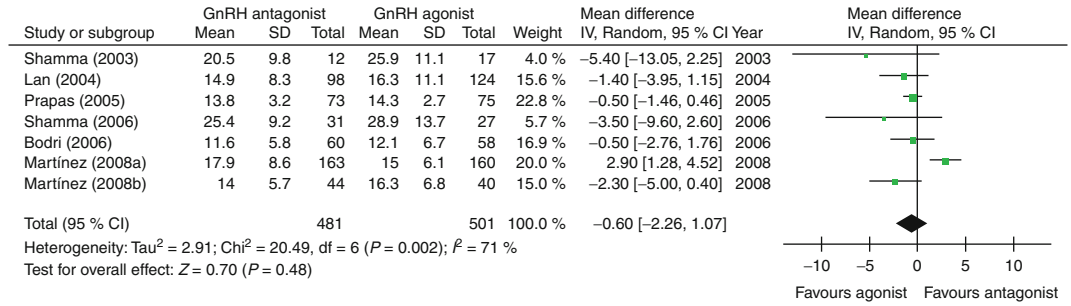

Fig. 16.2 Weighted mean difference for the number of retrieved oocytes (Reprinted from Bodri et al. [35]. Copyright (2011), with permission from Elsevier)

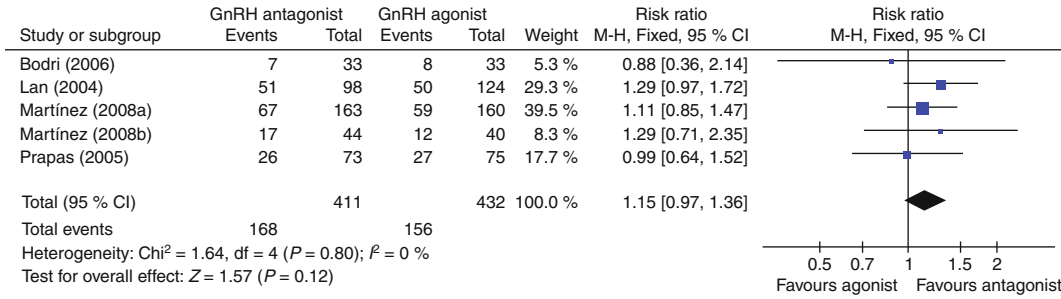

Fig. 16.3 Risk ratio for recipient ongoing pregnancy rate per randomized donor (studies with 1:1 donor-recipient ratio) (Bodri et al. [35])

unstimulated ovaries, comparable pregnancy rates (30 % live birth rates per cycle) were obtained compared to conventional donor IVF. Although this approach completely eliminates the risk of OHSS in the donor, the expected lower implantation rate of IVM embryos (18.2 %) hampers success rate in the recipient's cycle. Similarly, a single case report proposed the modified natural cycle IVF protocol in a 36-year-old donor by obtaining a healthy live birth in the recipient following single embryo transfer [37]. Although this approach eliminates any potential OHSS risk, it is hampered by the high risk of cycle cancellation and the failure of retrieving any mature egg from the donor.

Cycle Cancellation

Cycle cancellation by withholding hCG trigger practically eliminates the risk of any clinically significant OHSS but with the great drawback of also cancelling the recipient's cycle. Because spontaneous ovulation could still occur, cancelled donors should use efficient and reliable barrier contraception methods to avoid the risk of any unwanted pregnancy and subsequent late-onset OHSS.

Coasting

Coasting efficiently reduces the incidence and severity of OHSS both in oocyte donors and in non-donor IVF patients. It must be emphasized however that OHSS is not completely prevented and that prolonged coasting >4 days compromises oocyte quality and subsequent embryonic implantation rates [38, 39]. Recent data shows that in oocyte donor cycles where GnRH agonist trigger was used, elevated peak estradiol can be tolerated and coasting becomes unnecessary [40, 41].

Antagonist Coasting

In a randomized clinical trial of high OHSS-risk non-donor IVF patients stimulated with a long

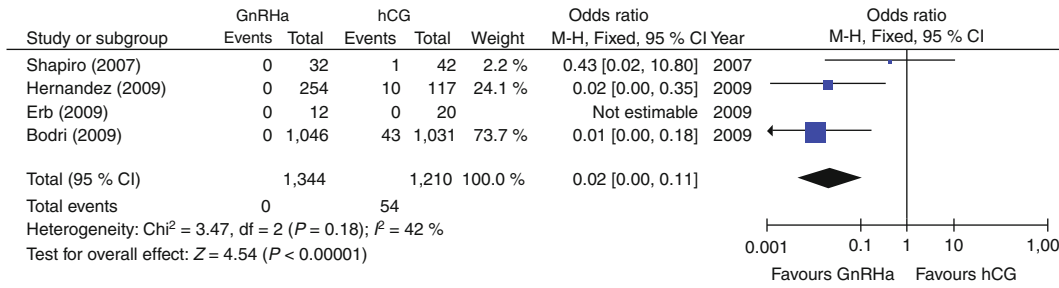

Fig. 16.4 OHSS incidence in oocyte donors after triggering with GnRHa versus hCG: retrospective cohort studies

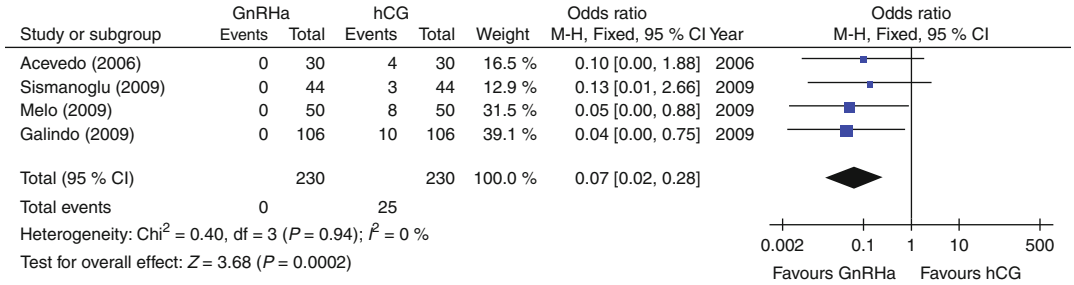

Fig. 16.5 OHSS incidence in oocyte donors after triggering with GnRHa versus hCG: randomized clinical trials

agonist protocol GnRH, antagonist coasting has resulted in more rapid estradiol decline, shorter coasting duration, and a higher number of good quality embryos compared to conventional coasting [42]. Although this method is readily applicable in oocyte donors stimulated with the agonist protocol, the exact degree of OHSS reduction or any potential deleterious effect on oocyte quality has yet to be evaluated in a larger trial.

Reduced hCG Dose

A recent systematic review that included a limited number of clinical trials concluded that in the high-risk non-donor IVF patient population, the incidence of OHSS was not reduced even with lower dose of urinary hCG (5,000 versus 10,000 IU) [43].

GnRH Agonist Triggering: Achieving an OHSS-Free Stimulation Protocol

Several retrospective cohort studies [40, 44–46] evaluated the outcome of oocyte donation cycles after the newly available GnRH agonist trigger. Although they varied largely in size (ranging from 32 to 2,077 cycles), all of them were concordant in finding no significant differences in key outcome variables such as the proportion of mature oocytes, fertilization rates, and subsequent recipient implantation and pregnancy rates. More importantly, no moderate/severe OHSS cases at all were detected after agonist trigger, whereas in the hCG group, its incidence reached 4.5 %. These retrospective series had an inherent bias between the examined treatment groups because agonist triggering was preferentially applied to cycles with a much higher ovarian response (Fig. 16.4). A number of methodologically more appropriate randomized clinical trials [47–50] have evaluated the same variables as retrospective series. They included a total number of oocyte donors ranging from 60 to 212 per study. No significant difference was observed in the number of retrieved oocytes (total and mature), fertilization rates, embryo quality, and pregnancy rates in corresponding recipients. OHSS cases only occurred in the hCG arm (between 7 and 16 %) (Fig. 16.5). This means that calculated OHSS reduction rates

after GnRH agonist triggering are especially high (OR 0.02–0.07) unparalleled by any other OHSS prevention method. A recent observational follow-up study performed in 102 high OHSS-risk oocyte donors examining biochemical and ultrasound signs of early-onset OHSS has even suggested the complete elimination of the syndrome (absence of hemoconcentration or ascites) after agonist triggering [41]. Moreover, data from both retrospective cohort studies and controlled clinical trials suggests that GnRH agonist triggering does not adversely affect the quality of retrieved oocytes or the implantation potential of resulting embryos. These findings suggests that GnRH agonist triggering is currently one of the most efficient and powerful ways of preventing OHSS in oocyte donors. However, excessive stimulation is still not recommended due to more discomfort and a higher risk of oocyte retrieval-related complications.

Intravenous Fluids

Although intravenous albumin administration for preventing the development of severe OHSS was first suggested almost two decades ago, clinical studies on its effectiveness still show conflicting results. A recent meta-analysis has concluded that currently there is limited evidence of the benefit of intravenous albumin at the time of oocyte retrieval. In contrast, hydroxyethyl starch markedly reduced (OR 0.12, 95 % CI 0.04–0.40) severe OHSS incidence in non-donor IVF patients [51].

Luteal-Phase GnRH Analogues

A recent, pilot study performed in 28 oocyte donors evaluated the luteal-phase administration of GnRH analogues (either GnRH agonists or antagonists) during 9 days following oocyte retrieval [52]. Although the only significant finding was a reduction in the amount of free pelvic fluid measured in the Douglas pouch, the authors suggested that both analogues are capable of inducing a pronounced luteolysis evidenced by a decrease in serum VEGF levels. In addition, this strategy has also been used in non-donor IVF patients undergoing freezing of all embryos or fresh embryo transfer [53].

Dopamine Agonists

Dopamine agonists used after hCG administration were recently proposed as a prophylactic treatment for OHSS prevention. A recent meta-analysis pooled the findings of four randomized clinical trials [54]. Although there was a significant reduction in overall OHSS incidence, it was only observed in the early-onset (OR 0.10, 95 % CI 0.03–0.33) and moderate OHSS (OR 0.38, 95 % CI 0.22–0.68) groups. A pilot trial successfully applied this strategy in high-risk oocyte donors achieving a significant albeit not complete reduction in moderate OHSS rates (from 44 to 20 %) [55].

Aromatase Inhibitors

Letrozole—an efficient oral aromatase enzyme inhibitor—was administered to oocyte donors during their luteal phase in two recent pilot studies causing a rapid, dramatic decrease in serum estradiol levels [56, 57]. Although OHSS incidence was not evaluated in these studies, it was suggested that letrozole could be used as an adjuvant to reduce supraphysiological estradiol levels in high-responder IVF patients, diminishing the risk of potential thromboembolic complications.

General Recommendations

Among the currently available preventive methods, only GnRH agonist triggering comes close to an almost complete (if not 100 %) prevention of early-onset OHSS. Antagonist coasting, luteal-phase administration of GnRH analogues, and/or dopamine agonists seem to be promising pharmacological strategies. Other methods have either limited or no efficiency (such as simple coasting, reduced hCG dose, intravenous albumin) or their effect has not been tested yet in sufficiently

Table 16.3 OHSS prevention methods in oocyte donors

OHSS prevention method	Advantages	Drawbacks
In vitro maturation	Complete prevention	Low embryo implantation rate
Cycle cancellation	Complete prevention	Cancelled recipient cycle, expensive
Coasting	Cheap	Incomplete prevention, compromised oocyte quality if prolonged >4 days
Antagonist coasting	Can be used in agonist protocol	Efficiency is not yet proven, expensive
Reduced hCG dose	Cheap	Inefficient
GnRH agonist triggering	Complete prevention	Only applicable in GnRH antagonist protocols
Intravenous albumin	–	Limited efficiency, potential side effects
Luteal-phase GnRH analogues	Can be used in agonist protocol	Efficiency is not yet proven, expensive
Dopamine agonists	Oral administration	Incomplete prevention, potential side effects
Aromatase inhibitors	Oral administration	Efficiency is not yet proven, expensive

large-sized clinical trials (IVM, HES, aromatase inhibitors) (Table 16.3).

Hence, in the context of oocyte donation, the first choice option is GnRH antagonist stimulation protocol coupled with GnRH agonist triggering. It is easily applicable in all donors independent of their ovarian response (both high and normoresponders), and according to available evidence, it does not adversely affect recipient cycle outcome. The application of GnRH agonist triggering has also important practical consequences. Given the fact that OHSS risk is greatly diminished or even eliminated, cycle monitoring could become less stringent (i.e., less need for repetitive estradiol assays or ultrasound monitoring), and in the future, stimulation surveillance could probably be simplified even further. In addition, after GnRH agonist triggering, cycle cancellation, or co-interventions, reducing OHSS risk (such as coasting) may become entirely unnecessary [40]. All these positive effects would allow a reduction in the workload of medical teams and greatly simplify the everyday management of oocyte donation cycles. Additional benefits include the shorter duration of the unsupported luteal phase (4–6 days), reduced ovarian volume, and diminished abdominal distension which altogether might substantially decrease the burden of treatment for oocyte donors [58, 59].

If for some well-defined reason (such as suboptimal outcome in a previous GnRH antagonist-treated cycle) choosing an antagonist protocol is not an option, a GnRH agonist protocol (long or short) with reduced FSH dose and mandatory hCG triggering might be recommended. Nonetheless, in high-risk patients with high follicular counts and elevated peak estradiol levels, antagonist coasting and/or luteal-phase GnRH analogue/dopamine agonist administration is also recommended.

Diagnosis and Management of OHSS in Oocyte Donors

In a recent review, a new practical and clinically oriented OHSS grading system was proposed based on more objective measurements compared to those that were previously established [23] (Table 16.4). The authors concluded that subjective OHSS symptoms show large individual variations and cannot be assigned to a particular OHSS grade. In contrast, transvaginal ultrasound is particularly useful in determining the extent of fluid shift into the pelvis and abdomen [41, 55]. Whereas mild OHSS can be accompanied by the presence of a small amount of liquid in the pouch of Douglas, the moderate form is characterized by a larger periuterine collection. Severe OHSS is characterized by observing large amount of ascites between the intestinal loops. Additionally, hemoconcentration (hct>45 %) remains a very useful objective marker in detecting clinically significant moderate/severe OHSS which needs close attention and might require hospitalization.

Table 16.4 Proposed new clinical grading system for OHSS

	Mild	Moderate	Severe
Objective criteria			
Fluid in Douglas pouch	✓	✓	✓
Fluid around uterus (major pelvis)		✓	✓
Fluid around intestinal loops			✓
Hematocrit >45 %		✓[a]	✓
White blood cells >15,000/mm		±[a]	✓
Low urine output <600 mL/24 h		±[a]	✓
Creatinine >1.5 mg/dL		±[a]	±
Elevated transaminases		±[a]	±
Clotting disorder			±[b]
Pleural effusion			±[b]
Subjective criteria			
Abdominal distention	✓	✓	✓
Pelvic discomfort	✓	✓	✓
Breathing disorder	±[c]	±[c]	✓
Acute pain	±[c]	±[c]	±[c]
Nausea/vomiting	±	±	±
Ovarian enlargement	✓	✓	✓
Pregnancy occurrence	±	±	✓

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Note: The ± sign means may or may not be present
[a]If two of these are present, consider hospitalization
[b]If present, consider intensive care
[c]If present, consider hospitalization

As mentioned before, oocyte donors are only exposed to early-onset OHSS, and due to non-conception, the spontaneous resolution of the syndrome is expected after menstruation occurs. First symptoms usually appear 3–9 days after hCG administration but can persist up to 10–12 days afterward. This relatively benign outcome means that oocyte donors can usually be managed on an outpatient basis [60]. Nonetheless, if signs of potentially life-threatening severe OHSS are detected, such as oliguria, pleural effusion, or clotting abnormalities, hospitalization with more aggressive treatment options (thrombophylaxis, culdocentesis, and intensive care) are recommended [23].

In relation to the recently emerged option of substituting the hCG trigger, there is some debate in the literature as to whether clinically significant early-onset OHSS will occur at all after GnRH agonist triggering [61, 62]. In fact, following agonist trigger, a massive, irreversible luteolysis can be seen, and menstruation usually occurs 4–6 days after oocyte retrieval. Therefore, it is more likely that any early alarming symptoms (e.g., abdominal distension, pain, nausea, vomiting) occurring during this relatively short time period are likely related to ovarian retrieval-related complications rather than to "real" OHSS or at the most represents some kind of "aborted" clinical picture of moderate OHSS [41].

Potential Long-Term Consequences of Oocyte Donation

The link between ovulation-stimulation drugs and the risk of future reproductive cancers (e.g., ovary, breast, and endometrium) has been extensively studied, but any potential relationships are still poorly understood. Although most studies failed to demonstrate a "cause and effect" relationship and were somewhat reassuring, it seems that among infertile patients there may be an increased risk for ovarian cancer among nulliparous

women, particularly those patients with extensive pelvic problems related to endometriosis and chronic PID. Such patients also appear at risk for developing *borderline* ovarian tumors [63]. However, infertility itself is a strong inherent confounding factor which might only be controlled for by examining data on cancer incidence of fertile oocyte donors. Information is extremely scarce on the risk of tumors in women who underwent ovarian stimulation for oocyte donation. To date, only three case reports have been published, reporting the occurrence of colon and breast cancers a few years after individuals had participated in oocyte donation [64].

Similar to the debate regarding cancer risk, there is very limited data on the risk of developing future infertility in former oocyte donors. In a recent European study, 194 former egg donors were questioned regarding their fertility an average of 3.7 years after their stimulation cycle. The authors found that most women (95 %) who wanted to have children conceived spontaneously within a period of 12–18 months, suggesting that the donation procedure did not affect their subsequent fecundity [17]. Another retrospective study evaluated successive cycle outcomes in consecutive oocyte donation attempts up to nine cycles and concluded that ovarian response was maintained throughout [65]. These findings suggest that a stimulation-related decrease in ovarian reserve is unlikely.

With relation to potential short- and long-term consequences and also to reduce the risk of consanguinity among donor-conceived offspring, it is reasonable to set limits for oocyte stimulation cycles performed by the same donor. Currently, there are but few well-defined guidelines which are specifically related to oocyte donors. The American Society for Reproductive Medicine issued a practice guideline focused on repetitive oocyte donation in order to limit health risks to the oocyte donor [66]. They suggested that limiting the donor's participation to six stimulated cycles would be reasonable. In fact, a similar European guideline was also issued by the regional Health Authority in Barcelona, Spain, which fixed similar limit of oocyte retrievals per donor. Both in the USA and in Europe, there is an increasing awareness of possible short-term complications as well as for the need of long-term follow-up of oocyte donors [64, 67]. Hopefully, in the near future, governmental agencies and professional societies will start to work together in establishing compulsory donor registries which will permit conducting large-scale follow-up studies and could help to answer some of the remaining open questions about the long-term consequences of oocyte donation.

Editor's Commentary

We now know, and most ART practitioners generally believe, that egg donation is a reasonable risk activity and may be offered to healthy women who wish to participate. It certainly was not so obvious to us in the early 1980s, and in fact, the risks that were assumed by the human subjects agreeing to perform embryo donation at the Harbor-UCLA Medical Center would be considered unacceptable by today's standards. The first donors were only paid $250 to be inseminated with unprocessed ejaculated semen and then underwent a series of uterine lavages in hope of recovering the in vivo fertilized embryo! It is really incredible that no one was seriously injured in the initial efforts.

Comparatively, today's donors are much better off, even though they now typically undergo anesthesia in order to recover their eggs. The risks are largely no different than those faced by any patient undertaking ovarian hyperstimulation and egg retrieval for autologous use. The obvious issue thus becomes whether or not it is ethical to perform a procedure upon a young woman that carries a definable risk of injury for no known personal benefit other than payment for services rendered. This remains a contentious and hotly debated subject which has been present since the very first case and continues unabated today.

Daniel Bodri, M.D., provides a nice review of the published literature spanning three decades and multiple continents and defines the low risk of complications noted

in egg donors. More importantly, he summarizes several approaches which promise to further lower the risk. OHSS remains the biggest worry, and advances in screening, such as obtaining precycle serum AMH levels, and in the clinical practice, using GnRH triggers instead of hCG, offer hope for dramatically lowering the complication rate. Even so, we must not forget that the health and well-being of our egg donors must be as vigilantly safeguarded as our regular patients. It is therefore important to openly share and discuss all complications, both actual and theoretical, with these young women prior to their participation. I prefer to lose an occasional potential donor to fear and anxiety after hearing the procedural details than to have any one of them look back with regret and feel that they were taken advantage of by the medical system.

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