

Chapter 17

Risks of Natural Cycle and Minimal Stimulation IVF



Michael von Wolff

17.1 Background

In addition to the success of IVF therapy, its risks also play a significant role. Couples are most concerned about the possible effects of hormone stimulation on the woman's health and psyche. From a reproductive medicine point of view, the risks of overstimulation syndrome with all the associated complications as well as the risks of follicle aspiration play the largest role.

When deciding on the various IVF therapies, it is important to bear in mind that the risk of overstimulation is greatest with conventional IVF, while the risk of follicular aspiration is probably more relevant with natural cycle IVF (NC-IVF) and minimal stimulation IVF, as more oocyte pick-ups are required on average.

The risks of IVF therapy for the health of children are also relevant. The effect on children's health is dealt with in Part V of this book, "Children's health."

17.2 Health Risks for Children

The IVF-related risks for children are dealt with in Part V of this book "Children's health." In Chap. 20, the malformation, obstetric and epigenetic risks are described and discussed, regardless of the type of IVF therapy. Chapter 21 describes specifically the child health risks associated with NC-IVF. Part V is concluded by Chap. 22 in which the risks of asthma and, in connection with this, the frequency of breast feeding in the different IVF therapies are presented.

M. von Wolff (✉)

Division of Gynecological Endocrinology and Reproductive Medicine, University Women's Hospital, University of Bern, Bern, Switzerland

e-mail: Michael.vonwolff@insel.ch

17.3 Risks of Ovarian Hyperstimulation Syndrome (OHSS)

OHSS was a feared complication, especially during the early years of IVF therapy. The goal at that time was to obtain as many oocytes as possible. Later it was found out that the cumulative success rate did not increase further with a very large number of oocytes which led to a reduction in the gonadotropin doses used and thus also to a reduction in OHSS rates. Another important step was the introduction of GnRH antagonist protocols, which were associated with a lower risk of OHSS compared to long-acting GnRH agonist protocols. According to a meta-analysis by Yang et al. (2021) [1] (Table 17.1), that included studies from 2015 to 2018, the risk of OHSS is increased with long-acting GnRH agonist protocols, with a relative risk of 1.63 (95% CI: 1.15–2.32). In the included studies, OHSS rate varied in the long-acting GnRH agonist group from 3.1% to 46.2%, whereas in the antagonist group, the rate varied from 2.0% to 21.1%.

A further decrease in risk results from the “freeze all” strategy and the use of GnRH agonists to trigger ovulation, which are used in cycles with an increased risk of OHSS [2].

With NC-IVF and minimal stimulation IVF therapies, the risk of OHSS is practically non-existent due to a low number of follicles.

17.4 Risks of Oocyte Pick-Up

The risk of a pelvic infection as a result of the follicle aspiration is very low and is less than 1% (Table 17.2).

The risk of relevant vaginal bleeding, which requires longer compression or tamponade, is also very low and is <1% (Table 17.2). More clinically relevant are the risks of bleeding into the abdomen leading to hemoperitoneum. In the study by Levi-Setti et al. (2018) [3], the risk of hemoperitoneum per oocyte pick-up was 0.23%, and 35% of these cases subsequently required laparoscopy or laparotomy.

Bleeding leading to a hemoperitoneum or peritoneal hematoma is probably often the cause of severe pain, requiring hospitalization, which occurs in <1% of follicle aspirations (Table 17.2).

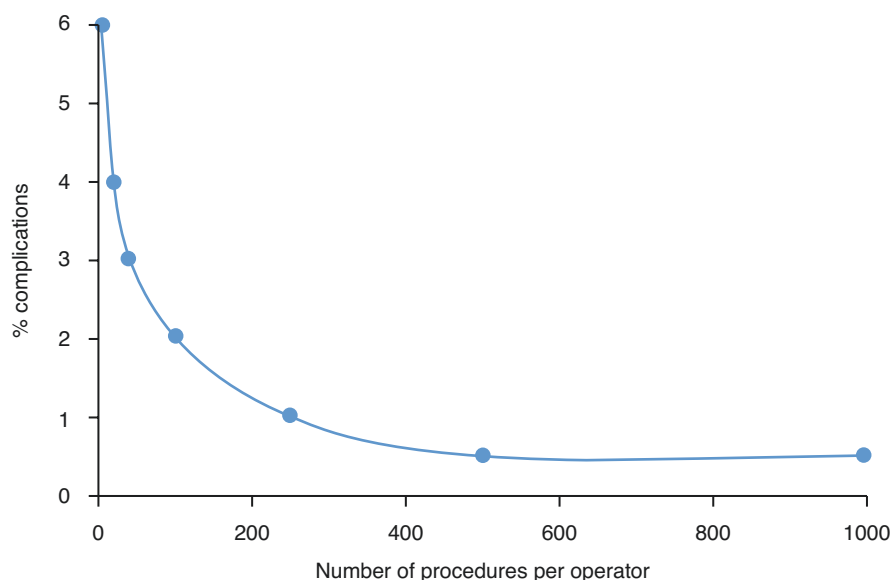
Table 17.1 Risk for OHSS in women treated with long-acting GnRH agonists versus GnRH antagonists (Summary of a meta-analysis [1])

Included studies	GnRH agonist cycles: Events/total, <i>n</i>	GnRH antagonist cycles: Events/total, <i>n</i>	Risk ratio (95% CI)	Heterogeneity, <i>I</i> ²
7 studies, overall result	99/1769	62/1434	1.63 (1.15– 2.32)	0% ^a

^aIndicates very low heterogeneity of studies (www.handbook-5-1.cochrane.org)

Table 17.2 Complications observed due to follicle aspiration in patients undergoing IVF treatments

	Levi-Setti et al. (2018) [3]	Özaltın et al. (2018) [4]	Ludwig et al. (2006) [5]
Number of oocyte pick-ups	23.827	1.031	1.058
Pelvic infections	10 (0.04%)	8 (0.77%)	0
Major vaginal bleeding	2 (0.01%)	7 (0.7%)	1 (0.1%)
Hemoperitoneum	54 (0.23%)	No data	No data
Severe pain, requiring hospitalization	14 (0.6%)	1 (0.09%)	7 (0.7%)

**Fig. 17.1** Rate of surgical complications for single operator (% complications) versus number of procedures (follicle aspirations). Adjusted according to [3]

It should be noted that data about the risk of follicle aspirations are derived exclusively from conventional IVF therapies. Conventional IVF therapies are usually accompanied by a polyfollicular response, so that a large number of follicles are aspirated. Serum estradiol (E2) concentrations are also very high, which dilates the veins of the vaginal wall and pelvis, increasing the risk of bleeding. Finally, it is important to note that the studies used large-volume aspiration needles such as 16G [4, 5] or 17G [3], which are associated with greater tissue trauma and therefore a higher risk of bleeding.

Levi-Setti et al. (2018) [3] also evaluated whether the surgeon's experience played a role in the incidence of complications (Fig. 17.1). They found that the incidence was significantly higher for physicians who had performed <250 retrievals compared with those who had completed >250 retrievals (OR 0.63, 95% CI: 0.40–0.99).

17.5 Risk and Need Assessment in Different IVF Treatments

There is practically no risk of OHSS with NC-IVF or minimal stimulation IVF treatment. On the other hand, more treatment cycles are carried out on average until pregnancy occurs, and therefore more aspirations are performed (see Chap. 19). The more oocyte retrievals are performed, the higher the risk of infection or bleeding.

However, it should be noted that the risks from follicle aspirations in NC-IVF or minimal stimulation IVF treatment may be lower than in conventional IVF treatment.

In NC-IVF and minimal stimulation IVF, only one to very few follicles are aspirated. The E2 concentrations are also much lower, and the aspiration needles are much thinner. The aspiration needles used in the IVF centre in Bern, Switzerland have a volume of 19G, needles in the Kato Ladies Clinic in Tokyo and New Hope infertility Centre in New York have a volume of 21G (see Chap. 13).

It can therefore be assumed that the risk of complications is much lower in aspirations performed in NC-IVF and minimal stimulation IVF treatments. Even though data regarding the risks has not yet been published for different IVF treatments, personal experiences confirm this assumption. In the IVF centre in Bern, Switzerland, only one hemoperitoneum was reported in a series of 5000 aspirations using 19G aspiration needles performed between 2009 and 2020. The reported hemoperitoneum required a laparoscopy and revealed bleeding from the punctured ovary but no other injury.

A systematic analysis of the risks of follicle aspiration in NC-IVF and minimal stimulation IVF compared to conventional IVF is currently performed in the IVF-Naturelle® network (see Chap. 24). Results are expected in 2023.

Each IVF technique is associated with therapy-specific risks. Since the overall risks are very low, these risks are usually not a criterion for or against performing one of the different IVF techniques.

However, awareness of complications should be present, and efforts should be made to minimize the risk of infection and bleeding. A worldwide web-based survey of 155 IVF centres in 55 countries, performing 97,200 IVF cycles annually, revealed that centres use different strategies to minimize risk. However, the types of strategies used are inconsistent [6].

The examples in this chapter show that a thin aspiration needle, paired with much experience with follicle aspirations, is likely to be a major key to risk reduction. An ESHRE working group provides good practice recommendations covering technical aspects of ultrasound guided transvaginal oocyte retrieval [7].

17.6 Practical Conclusions

- Each IVF therapy has therapy-specific risks.
- However, the risks (OHSS due to ovarian stimulation and infection or bleeding due to follicle aspiration) are very low.

- The risks are usually not a decision criterion when choosing the IVF technique.
- Nevertheless, efforts should be made to minimize the risks, whether by avoiding excessively high stimulation doses, using the antagonist protocol or thin aspiration needles.

References

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