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ORIGINAL ARTICLE *Infertility*

The number of oocytes retrieved during IVF: a balance between efficacy and safety

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STUDY QUESTION: What is the relationship between the number of oocytes collected in fresh IVF treatments and the likelihood of cumulative delivery rate (fresh and frozen) per oocyte aspiration, severe ovarian hyperstimulation syndrome (OHSS) and thromboembolic events?

SUMMARY ANSWER: Cumulative delivery rate per aspiration increases up to 20 oocytes retrieved and then evens out while the incidence of severe OHSS increases more rapidly from around 18 oocytes and thromboembolic events, although rare, occurs in particular if 15 or more oocytes are retrieved.

WHAT IS KNOWN ALREADY?: Previous studies have shown that the number of oocytes retrieved for IVF is a positive predictor of live birth in fresh cycles. Few studies have investigated cumulative live birth rates and OHSS in relation to the number of aspirated oocytes.

STUDY DESIGN, SIZE, DURATION: Retrospective population-based registry study including 39 387 women undergoing 77 956 fresh IVF cycles in the period 2007–2013 and 36 270 consecutive transfers of frozen/thawed embryos in the period 2007–2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Data from The Swedish National Quality Registry of Assisted Reproduction (Q-IVF) including all IVF cycles with oocyte retrieval performed in public or private infertility clinics during the study period, was cross-linked to the National Patient Register regarding diagnostic codes (ICD 10) for severe (OHSS) and thromboembolic events. Oocyte donation cycles were excluded.

MAIN RESULTS AND THE ROLE OF CHANCE: Live birth delivery rate in fresh cycles increased up to 11 oocytes retrieved and then evened out, where the live birth rate was 30.3% for a 34-year-old woman. The cumulative delivery rate per aspiration, including fresh transfer and all subsequent transfers of frozen-thawed embryos (FET cycles) per oocyte retrieval, increased up to approximately 20 oocytes where it reached 45.8%. The adjusted odds ratio (AOR) for live birth by the number of oocytes was 1.064 (95% CI: 1.061; 1.067). The incidence of severe OHSS increased significantly by the number of oocytes, particularly if more than 18 oocytes were retrieved. The AOR for OHSS by the number of oocytes was 1.122 (95% CI: 1.08; 1.137). Thromboembolic events were rare, a total of 16 events in 14 patients were observed, and occurred in particular if 15 or more oocytes were retrieved.

LIMITATIONS, REASONS FOR CAUTION: All FET cycles might not be included. Some embryos cryopreserved between 2010 and 2013 might still result in additional births until 2018. Furthermore the gonadotrophin dose was not included in the Q-IVF Registry in the study period, thus adjustment for dose was not possible.

WIDER IMPLICATIONS OF THE FINDINGS: The results suggest a shift at approximately 18–20 oocytes where the cumulative delivery rate per aspiration levels off and, at the same time, the incidence of severe OHSS increases more rapidly. Thromboembolic events, although rare, should also be taken into consideration at stimulation regimes for IVF. Evaluating data taking both efficacy and the most serious safety aspects into account, is a new approach and of crucial importance both for patients undergoing IVF and their physicians.

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Key words: ovarian stimulation / IVF outcome / cumulative delivery rate / OHSS / thromboembolic events

Introduction

The overall aim in assisted reproductive treatment (ART) is to achieve a pregnancy leading to the birth of a healthy baby and with a minimum of side effects. Several cohort studies (van der Gaast *et al.*, 2006; Hamoda *et al.*, 2010; Sunkara *et al.*, 2011; Fatemi *et al.*, 2013; Ji *et al.*, 2013; Stanger and Yovich, 2013; Steward *et al.*, 2014) have shown that the number of oocytes retrieved for in vitro fertilization (IVF) is a positive predictor for live birth. Between 6 and15 oocytes have been found to be optimal for live birth in fresh cycles, with a lower live birth delivery rate if fewer oocytes are retrieved and a plateau (Hamoda *et al.*, 2010; Fatemi *et al.*, 2013; Stanger and Yovich, 2013; Steward *et al.*, 2014) or even a decrease (van der Gaast *et al.*, 2006; Sunkara *et al.*, 2011; Ji *et al.*, 2013) if a higher number of oocytes is retrieved. A high number of retrieved oocytes is also associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) (Ji *et al.*, 2013; Steward *et al.*, 2014). The incidence of severe OHSS reported in clinical studies varies from 2% (Papanikolaou *et al.*, 2006) to almost 9% (Toftager *et al.*, 2016). The categorization of OHSS is based on old references (Golan *et al.*, 1989; Navot *et al.*, 1992) not always applicable in modern daily practice and the term OHSS is widely used, ranging from mild discomfort to a severe condition demanding intensive care. Thromboembolic events are commonly associated with OHSS with a reported incidence of 1.7% in cycles leading to delivery (Rova *et al.*, 2012). In severe cases OHSS can develop into a life-threatening condition with an increased risk of thromboembolic events (Rova *et al.*, 2012) and, though rare, deaths have been reported (Mor and Schenker, 2014).

As single embryo transfer (SET) becomes more widespread (Ishihara *et al.*, 2015), particularly in the Scandinavian countries (Thurin *et al.*, 2004; McLernon *et al.*, 2010; Pandian *et al.*, 2013), more embryos are available for freezing and thawing. Freezing-thawing (FET) cycles now constitute a third of all IVF cycles performed yearly in Sweden, and children born from cryopreserved embryos represent around 25% of all ART children born annually (www.qivf.se). With an efficient freezing programme the cumulative pregnancy and live birth delivery rates per aspiration become increasingly important measures of efficacy. Most of the earlier studies investigating the impact of the number of oocytes retrieved on live birth delivery rate have considered only fresh cycles. A few studies from individual clinics, and with a limited number of patients included, have also analysed cumulative delivery rate (Ji *et al.*, 2013; Stanger and Yovich, 2013) after both fresh cycles and subsequently performed FET cycles. These studies have found that cumulative delivery rate per aspiration increases in line with the number of oocytes retrieved and there is no indication of a plateau at a certain number of oocytes.

The aim of this large, nation-wide Swedish study was to investigate the effect of the number of oocytes retrieved on live birth delivery rate resulting from fresh IVF cycles and cumulative delivery rate after one fresh and all subsequent FET cycles from one oocyte retrieval. In addition we wanted to investigate the relationship between the number of oocytes retrieved and the serious, potentially life threatening, side effects severe OHSS and thromboembolic events.

Material and Methods

Data was collected from The National Quality Registry of Assisted Reproduction (Q-IVF) for the years 2007–2014. All fresh cycles performed in Sweden from 2007 to 2013, with subsequent FET cycles performed from 2007 to 2014 were included. Oocyte donation cycles were excluded. Swedish legislation allows embryos to be cryopreserved for 5 years after retrieval, however few embryos are cryopreserved for more than 1 year if delivery of a baby is not achieved. All IVF clinics, public as well as private, report their results to Q-IVF and the results are public and posted on the Q-IVF website. All patients are informed about the Q-IVF registry and may choose not to have their data included, although this is very rare.

Data collected from the Q-IVF included the woman's personal security number, type of IVF (fresh conventional IVF, fresh ICSI, frozen-thawed cycles), number of oocytes retrieved, date of oocyte retrieval, date of embryo transfer, number of embryos transferred, number of embryos frozen, date of embryo freezing, number of embryos thawed, date of thawing, live birth and date of delivery. A live birth was defined as the delivery of at least one live child. Cumulative live birth was defined as the number of women with at least one child born alive after one oocyte retrieval, thus including one fresh and all FET cycles from this oocyte retrieval and divided by all women going through oocyte retrieval during a certain period of time.

Patients were treated in either a GnRH agonist or antagonist protocol, and ovarian stimulation was performed with recombinant or urinary derived gonadotropins. Oocyte retrieval and fertilization with conventional IVF or ICSI followed standard techniques. In the vast majority of cycles (77% for fresh cycles and 92% for FET cycles in 2013) single embryo transfer (SET) was performed and more than two embryos were never transferred. Embryo transfer took place at the cleavage stage (Day 2 or 3) or at the blastocyst stage. FET cycles were performed in natural cycles or in hormone-stimulated cycles. The primary analysis of live birth delivery rate per fresh cycle included all fresh cycles with oocyte retrieval. We further performed an analysis, excluding cycles where all embryos were cryopreserved and thus no fresh embryo transfer took place. The most common reason for this procedure is threatening OHSS. Another, less common, reason might be fertility preservation of gametes or embryos in patients with malignant disease.

Data from Q-IVF for the time period 2007–2013 was cross-linked with the Swedish National In-patient Register, which includes information on all in-patient, care in Sweden. The Register was launched in 1964, reached full coverage in 1987 and was validated in 2011 (Ludvigsson *et al.*, 2011). The ICD 10 (International Statistical Classification of Diseases and Related Health Problems—Tenth Revision) codes for OHSS, and thromboembolic events were used. Data from Q-IVF was cross-linked with the Swedish National In-patient Register for the ICD 10 code N98.1 for severe OHSS, and the ICD 10 codes: I21, I26, I63, I65, I66, I67.6, I74, I80.1, I80.2, I80.3, I80.8, I80.9, I81, I82, H34, K55.0, O22.3, O22.5, O22.8, O22.9 and N28.0 for thromboembolic events. In this study we have chosen only to include patients with OHSS needing hospital care, to avoid inclusion of milder

conditions. The vast majority of severe OHSS cases are hospitalized and are consequently registered in the National In-patient Register. Thus, cross-linking the In-patient Register with the Q-IVF Registry gives reliable data on the correlation between the number of oocytes retrieved and the incidence of severe OHSS. On the other hand, thromboembolic events are occasionally treated in out-patient units hence, for the ICD 10 codes concerning these conditions, the cross-linking also included the Out-patient Register.

Ethical approval

The study was approved by the Regional Ethics Committee at Gothenburg University, D nr 811–14.

Statistical analysis

To explore the association between the number of retrieved oocytes and live birth delivery rate as well as cumulative delivery rate per aspiration and complications, a general estimation equation (GEE) was used, adjusting for dependence within each woman. Crude odds ratios (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI) for live birth after fresh cycle, and cumulatively after fresh and subsequent FET cycles, were calculated. OR and AOR with 95% CI were also calculated for OHSS after fresh cycle. Adjustments were performed for maternal age, year of treatment, previous failed cycles, previous IVF children and fertilization method used (conventional IVF/ICSI). The best models to represent number of oocytes (linear, second degree, or third degree polynomial, respectively) were decided using Hosmer–Lemeshow tests and visual inspections. OHSS was also assessed when the number of oocytes was categorized. Chi-square and Fisher's exact test were used for significance testing. For the association between the number of oocytes retrieved, divided into four groups, and the number of thromboembolic events, a Chi-square analysis for trend was performed. A *P*-value less than 0.05 was considered significant.

Results

During the study period 2007–2013, oocyte retrieval was carried out on 39 387 women and 77 956 fresh IVF procedures were performed. Patient and cycle characteristics are summarized in Table I. From 2007 to 2014, these oocyte retrievals generated 36 270 FET cycles. The median number of oocytes retrieved was nine (interquartile range 5–12) and the distribution of oocytes retrieved is shown in Fig. 1.

Table I IVF/ICSI data characteristics at cycle and woman level, respectively (Sweden 2007–2013).

Characteristics (cycle level)	*N* = 77 956 *n* (%)
Maternal age	
18–34 years	39 555 (50.7)
35–37 years	18 404 (23.6)
38–39 years	11 068 (14.2)
40 years and over	8929 (11.5)
Previous failed fresh cycles	
0	40 157 (51.5)
1	18 921 (24.3)
2	9930 (12.7)
3 or more	8948 (11.5)
Any previous IVF child	5083 (6.5)
Treatment type	
IVF	39 226 (50.3)
ICSI	37 886 (48.6)
Oocytes retrieved	
Median [IQR]	9 [5–12]
Year of cycle start	
2007–2009	31 912 (40.9)
2010–2011	23 057 (29.6)
2012–2013	22 987 (29.5)
Maternal age at first IVF treatment (woman level)	*N* = 39 387
18–34 years	22 493 (57.1)
35–37 years	8637 (21.9)
38–39 years	4543 (11.5)
40 years and over	3714 (9.4)

Association between the number of oocytes and live birth

Table II shows the results from crude and multivariable GEE analyses in which 'number of oocytes retrieved' was entered as a linear, continuous variable. Covariates significantly associated with live birth are given in the table. The results from the multivariable analysis (in which all the listed variables were entered simultaneously) were only marginally different from the crude analysis. In the multivariate model (Table II) a significant increase in cumulative delivery rate per aspiration was observed per oocyte retrieved (AOR 1.064, 95% CI: 1.061; 1.067). Maternal age, previous failed cycles and ICSI (vs. IVF) affected live birth delivery rate negatively while year of given treatment and live birth of a previous IVF child affected live birth delivery rate positively. Live birth delivery rate in fresh cycles increased up to 11 oocytes retrieved and then evened out, where the live birth rate was 30.3% for a 34-year-old woman. The cumulative delivery rate per aspiration, including fresh transfer and all subsequent transfers of frozen-thawed embryos (FET cycles) per oocyte retrieval, increased up to approximately 20 oocytes where it reached 45.8%.

Using quadratic models, the observed and the predicted curves for live birth delivery rate fitted well, both for fresh cycles and on a cumulative basis (Fig. 2). Live birth delivery rate increased by the number of oocytes in fresh cycles, reaching a plateau at 11–19 oocytes. When a higher number of oocytes were retrieved, a slight decrease in live birth delivery rate was noticed. The cumulative delivery rate per aspiration increased up to approximately 20 oocytes and then evened out. In 2178 out of 77 956 (2.8%) oocyte aspirations all embryos were cryopreserved. Excluding the 'freeze all' cycles changed the graph live birth delivery rate for fresh cycles slightly, particularly at high number of oocytes where no obvious decrease in live birth delivery rate was noted. The cumulative live birth delivery rate was of course not affected (Supplementary Information Fig. S1).

Association between the number of oocytes and serious complications

The total number of severe OHSS was 371 (0.5%). The incidence of severe OHSS increased significantly by the number of retrieved oocytes (Fig. 3) (AOR for one oocyte increase, adjusted for age:

1.122, 95% CI: 1.08; 1.137) (Figs 3 and 4). Adjustment for age changed the estimates only marginally (the crude estimate was 1.132, 95% CI: 1.118; 1.146). The increase had a steeper slope from 18 oocytes where the incidence was 1%, and reached 2.5% at 25 oocytes retrieved. The distribution of early vs. late OHSS is illustrated in Fig. 5. While early and late OHSS seemed to be equally common for patients with less than 15 oocytes retrieved, early OHSS was numerically more common when more than 15 oocytes were retrieved. Out of the 371 patients with severe OHSS, 171 (46.1%) achieved a live birth.

When categorizing the number of oocytes and assessing OHSS, significant higher OHSS incidence were found for each comparison (Fig. 5).

The total number of patients with thromboembolic events in the study population was 14. Two patients were registered for two thromboembolic events each, in the same fresh cycle, resulting in a total number of events of 16. In the statistical analysis 14 cycles with thromboembolic events are included. Thromboembolic events occurred most commonly when 15 or more oocytes were retrieved. In the group with less than 10 oocytes the incidence was 5/44 312 (0.01%), in the group with 10–14 oocytes, 2/20 287 (0.005%), in the group with 15–19 oocytes it was 5/8919 (0.06%) and in the group with more than 20 oocytes there were 4/3.898 (0.08% (*P* for trend ≤0.008)) (Fig. 6). About 8/14 (57.1%) of the patients with thromboembolic events had a live birth. A complete list of the thromboembolic events is presented in Supplementary Information Table S1. In some of the cases the location of the thrombosis is not specified. No thrombosis of the upper extremity was reported.

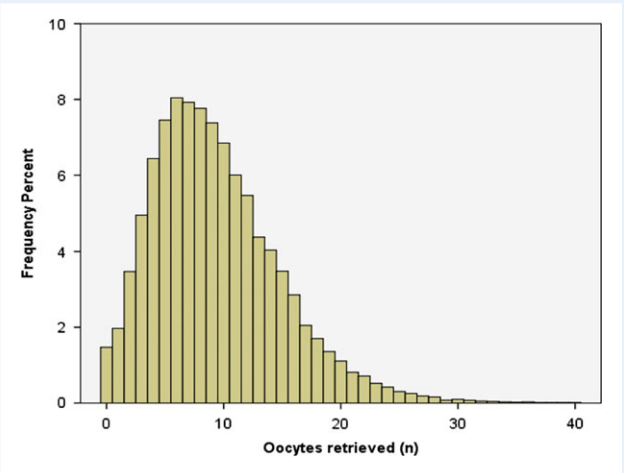

Figure 1 The distribution of aspirated oocytes. Median nine oocytes.

Discussion

The principal findings of this study were that live birth delivery rate after fresh cycles increased when up to 11 oocytes were retrieved and then levelled off while the cumulative delivery rate per aspiration rose up to at least 20 oocytes retrieved. This pattern was slightly changed for fresh cycles when excluding 'freeze all' cycles with an even higher live birth delivery rate at a higher number of oocytes. At the same time the rate of severe OHSS increased steadily in line with the number of oocytes retrieved, particularly if there were more than 18 oocytes. Hence there seems to be a shift in the balance between efficacy of treatment and patient safety regarding severe OHSS at approximately 18–20 oocytes where the possibility of freezing of all embryos and avoiding embryo transfer in the fresh cycle should be sincerely considered.

Thromboembolic events were rare and occurred primarily when 15 or more oocytes were retrieved.

The strength of the present study is the inclusion of complete data on all fresh IVF cycles performed in Sweden from 2007 to 2013, with no patients undergoing ovarian stimulation and oocyte retrieval being excluded. A further strength is that, in Sweden, a unique personal security number is given to all residents, enabling cross-linking of data between population and national quality registers.

A weakness of the study is that not all FET cycles may be included. Some embryos cryopreserved between 2010 and 2013 and still left in the freezer might result in additional births until 2018, although an analysis of FET cycles from the first years of the study period showed that few embryos were cryopreserved for more than 1 year. An additional weakness is that some cases of severe OHSS according to the classification by Golan *et al.*, (1989) and Navot *et al.*, (1992) might have been treated in out-patient units and thus not included in the Swedish National In-patient Register. Furthermore the gonadotrophin dose

Table II Odds Ratios for live birth considering both fresh and subsequent frozen cycles. Results from generalized estimating equations (GEE) analyses (linear models).

	Crude estimates		Estimates Multivariate model	
	OR	95% CI	OR	95% CI
Oocytes retrieved (per one step increment, linear model)	1.073	1.070–1.077	1.064	1.061–1.067
Maternal age (1 year increment)	0.923	0.920–0.926	0.936	0.932–0.939
Year (1 year increment)	1.021	1.013–1.029	1.031	1.022–1.039
Previous failed fresh treatments (one step increment)	0.866	0.855–0.877	0.900	0.888–0.912
Previous children with IVF (one step increment)	1.218	1.143–1.298	1.462	1.373–1.556
ICSI (vs. IVF)	0.839	0.812–0.866	0.819	0.792–0.846

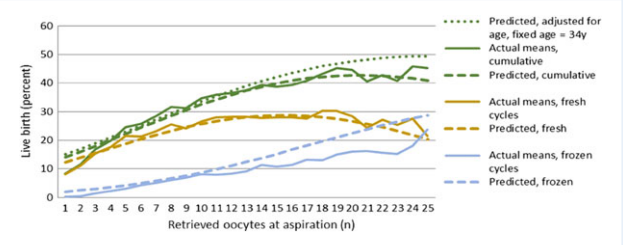

Figure 2 Percentage live birth in relation to the number of oocytes retrieved (considering fresh, subsequent frozen and cumulatively, respectively). Actual percentages and results from general estimation equations (GEE) analyses using models with one linear and one quadratic term. Adjustments were performed for maternal age, year of treatment, previous failed cycles, previous IVF children and fertilization method used (IVF/ICSI).

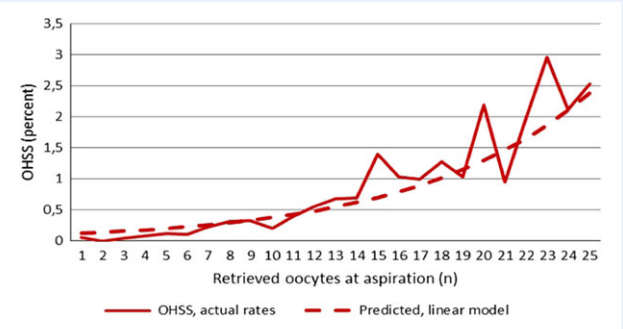

Figure 3 Percentage ovarian hyperstimulation syndrome (OHSS) (*y*-axis) in relation to the number of oocytes retrieved (*x*-axis) predicted and actual means.

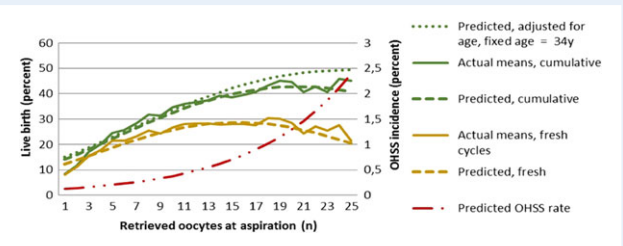

Figure 4 Percentage live birth in fresh cycles and cumulatively (left *y*-axis) and percentage OHSS (right *y*-axis) in relation to the number of oocyte retrieved.

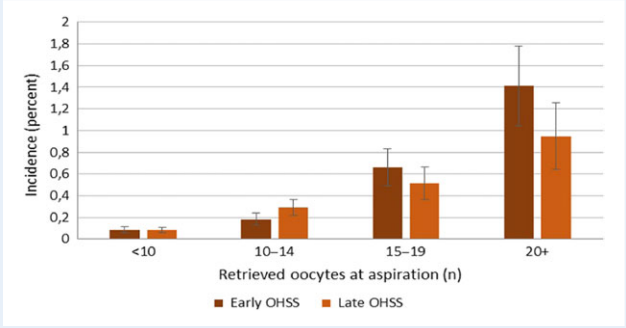

Figure 5 The incidence of OHSS by the number of retrieved oocytes (categorized) and divided into early cases (<9 days after oocyte retrieval) and late cases (≥10 days after oocyte retrieval), $P < 0.0001$ (Chi-square for trend). All oocyte categories, within early and late OHSS, respectively, differ significantly ($P < 0.0001$), Fisher's exact test.

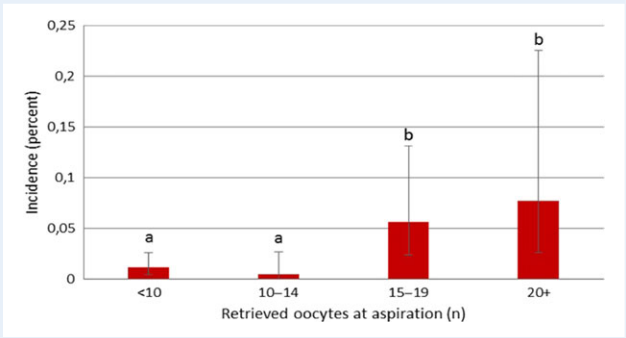

Figure 6 The incidence of thromboembolic events by the number of retrieved oocytes (categorized). Incidents and 95% confidence intervals (CI). $P = 0.008$ (Chi-square for trend). $P < 0.05$ (Unlike letters differ significantly, Fisher's exact test).

was not included in the Q-IVF Registry until 2010 and consequently it was not possible to adjust for this confounder during the study period.

Previous cohort studies based on national registers have mainly focused on efficacy (pregnancy or live birth) in fresh cycles (van der Gaast *et al.*, 2006; Hamoda *et al.*, 2010; Sunkara *et al.*, 2011; Fatemi *et al.*, 2013) and obstetric outcome after IVF (Finnström *et al.*, 2011; Sazonova *et al.*, 2011). Since the policy of single embryo transfer allows more embryos to be cryopreserved, and an increasing number of babies are born after FET cycles, the evaluation of cumulative efficacy data is becoming more relevant. In contrast to the present study, a recent Danish register study, published as an abstract at ESHRE 2017, investigating the relation between the number of oocytes retrieved and cumulative delivery rate per aspiration in the period 2002–2011 found that cumulative delivery rate per aspiration increased up to 15 oocytes retrieved with no improvement if a higher number of oocytes was retrieved (Malchau *et al.*, 2017). A possible explanation for the diverging results compared to the present study might be the different study periods. The results from the present study including data from 2007–2014 and showing that cumulative delivery rate per aspiration increased up to at least 20 oocytes might be explained by improved cryopreservation techniques in recent years, particularly vitrification of blastocysts.

In recent years the use of the freeze all procedure for prevention of OHSS has increased rapidly. Since the pathophysiological changes in the development of OHSS is mediated by hCG, the condition can to a high extent be prevented by using a short GnRH antagonist protocol for stimulation and a GnRH agonist for oocyte maturation triggering,

thus avoiding the administration of hCG (Melo *et al.*, 2009; Chen *et al.*, 2016). During the study period, the method used for oocyte maturation was almost exclusively injection of hCG. Though rare, severe cases of OHSS have been observed even after agonist triggering and cryopreservation of all embryos (Fatemi *et al.*, 2014; Gurbuz *et al.*, 2014). Dosage still has to be meticulously balanced, especially in young, lean patients with a presumed high ovarian reserve. Future studies on efficacy and safety including the impact of an increasing number of freeze all cycles will be of high value.

A few single-centre studies with a limited number of patients (Ji *et al.*, 2013; Stanger and Yovich, 2013) have evaluated cumulative live birth rates in relation to the number of oocytes collected, and one study (Ji *et al.*, 2013) have also assessed OHSS rates. The present study has expanded this concept by providing a large, complete national patient cohort, which evaluates live birth delivery rate and cumulative delivery rate per aspiration as well as the serious complications severe OHSS and thromboembolic events.

In conclusion, the balance between efficacy and safety during IVF stimulation in relation to the number of oocytes is a delicate issue. Results from this large registry study suggest that around 18 oocytes would be optimal from a cumulative live birth perspective, keeping severe OHSS at a reasonable level. Thromboembolic events are rare and occur mainly when 15 or more oocytes are retrieved. How to balance efficacy and safety is an important issue that should be discussed between patients and their physicians prior to IVF.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

All the authors contributed to the conception and design of the study and to the analysis and interpretation of data. All authors had full access to all the data and K.K. performed the statistical analysis. The results were interpreted by Å.M., K.K. and C.B. Å.M. and C.B. drafted the initial manuscript, reviewed by A.T.K. and finally approved by all authors.

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Conflict of interest

None declared.

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