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Annual incidence of severe ovarian hyperstimulation syndrome

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ABSTRACT

INTRODUCTION: Ovarian hyperstimulation syndrome (OHSS) is one of the major complications of assisted reproductive technology treatment. We assumed that it had declined in recent years owing to the options of new preventive strategies. The aim of the present study was to investigate the annual incidence of OHSS in Denmark in the course of a 17-year period.

METHODS: This was a national register-based historical cohort study including all women with an OHSS diagnosis admitted to Danish hospitals between 2001 and 2017. Data included information on all OHSS diagnoses, duration of hospital stay, early pregnancy complications and other complications like thromboembolism and ovarian torsion. The annual number of initiated stimulated in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) cycles was based on the annual reporting by the Danish Fertility Society.

RESULTS: From 2001 to 2017, a total of 2,261 (1.2%) women with an OHSS admission were identified among 186,168 stimulated IVF/ICSI cycles. The annual incidence of OHSS varied from 0.9% to 1.2-1.4% with no overall change over time (p = 0.24. Early OHSS (defined as OHSS without a pregnancy in the cycle) was seen in 48.5% of the events, late OHSS (defined as OHSS with a pregnancy in the cycle) in 51.2% of cycles. Among all women with OHSS, 75% were hospitalised for more than 24 hours, with mean 4.3 and 6.2 days in hospital for early and late OHSS, respectively.

CONCLUSIONS: The annual incidence of severe OHSS leading to a hospital admission remained stable for 17 years, which suggests that OHSS preventive actions like use of antagonist cycles, agonist triggering and freeze all should be better implemented in Denmark.

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Two major iatrogenic complications are related to assisted reproductive technology (ART): multiple gestations and ovarian hyperstimulation syndrome (OHSS). The former problem has, to a large extent, been solved through single embryo transfer. The second may be more difficult to reduce, but several advances in ART practices may potentially have reduced OHSS risk in recent years.

The OHSS-Free Clinic concept involves use of gonadotropin-releasing hormone (GnRH) antagonist protocols for ovarian stimulation, ovulation triggering with a GnRH agonist when an excessive number of follicles develop, and an embryo freeze-all approach [1-3]. Changing ovarian stimulation protocols from the long GnRH agonist towards the GnRH antagonist protocol should reduce the risk of OHSS by almost 50% [4-7]. On the other hand, the use of GnRH-agonist triggering in hyperresponsive patients should reduce the OHSS risk [3], and an embryo freeze-all approach may potentially eliminate the risk of late OHSS. Another improvement is the development of

predictive factors like anti-Mullerian hormone and antral follicle count, which may be used to determine the protocol; and gonadotrophin doses used, which may contribute to lower the risk of OHSS [8-12].

The aim of the present study was to investigate the annual incidence of OHSS in Denmark in the course of 17 years (2001-2017) based on the anticipation that we ought to see a reduction over time. Additionally, we analysed the prevalence of early and late OHSS, as they may be prevented differently. Finally, we aimed to characterise OHSS hospital admissions, concurrent complications and the prognosis for live birth in patients with late-onset OHSS.

METHODS

The study is a national register-based population study including all women with an OHSS diagnosis admitted to a Danish hospital from 2001 to 2017. The number of women with an OHSS diagnosis at the time of admission (International Classification of Diseases, tenth version (ICD-10), N98.1) was retrieved from the Danish National Patient Registry (NPR), along with information about age, date of admission and discharge, and complications possibly related to OHSS (**https://ugeskriftet.dk/files/a12190738_supplementary.pdf**.). The population was linked to the Danish ART Register by encrypted ID, and information was retrieved about initiation of the treatment cycle and oocyte retrieval dates. Data on pregnancy outcome in terms of abortions and deliveries in women with OHSS were retrieved from the NPR, the Danish Medical Birth Register and the Danish Miscarriage Register.

The number of annually initiated in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) cycles was retrieved from the Danish Fertility Society, which over the years have collaborated with the Danish ART register, which records all private and public Danish fertility treatments annually as from 2001.

OHSS was divided in two groups: early OHSS that was recorded as admission without a recorded pregnancy (non-pregnancy-related) and late OHSS that was recorded as an admission associated with a pregnancy diagnosis (pregnancy-related). The number of OHSS events was calculated per initiated treatment cycle. If a woman was hospitalised for OHSS more than once following the same treatment cycle, only the first incidence was included. The algorithm used for this recording was that if a woman had more than one OHSS admission diagnosis, it was only included once. Each OHSS diagnosis was coupled to the IVF treatment cycle recorded up to 60 days prior to the OHSS diagnosis. When a pregnancy was recorded in the NPR, Medical Birth Register or Miscarriage Register that could be linked to the cycle, the OHSS event was classified as late OHSS irrespective of whether the first admission occurred earlier than ten days after oocyte retrieval or not. The time to OHSS was calculated as the time (days) between oocyte retrieval and date of admission with an OHSS diagnosis.

Statistical methods

Annual incidence rates are presented as percentages of all stimulated ART cycles per year. Differences between the annual OHSS incidence rates and differences between groups of women with early and late OHSS were assessed by the χ^2-test or Fisher's exact test. Changes in rates by time were assessed using the Cochran-Armitage test for trend. In case of non-normality, means between groups were compared using the Mann-Whitney non-parametrical test. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed in SAS Enterprise Guide 7.1.

Ethics

The study was conducted by permission from the Danish Data Health Authority (R. No. 2006-41-6907) and reported to and approved by the regional data authority (Pacticus, the Capital Region of Denmark) as a research project: P-2020-217. Register studies in Denmark do not require approval from scientific ethics committees.

Trial registration: not relevant.

RESULTS

From 2001 to 2017, a total of 2,261 events were recorded. Overall, we found 1,096 cases of early OHSS (49.5%) where pregnancy was not achieved and 1,165 late OHSS (51.5%) where pregnancy was achieved (**Table 1**). We found no significant differences in the annual distribution over the years in early and late OHSS (p = 0.13). Furthermore, no trend for changes was observed in the distribution of early and late OHSS over 17 years (p = 0.26). The overall percentage of OHSS was 1.2% per initiated stimulated IVF/ICSI cycle (2,261 cases of 186,168 stimulated IVF/ICSI cycles). The incidence of OHSS ranged from 89 registered cases in 2002 to 157 cases in 2017. During the same period, the annual number of stimulated IVF/ICSI cycles increased from 8,805 in 2001 to 12,676 in 2017 (Table 1). The incidence of OHSS among all stimulated cycles thus ranged from 0.9% in 2002 to 1.4% in 2003 and 2005 (Table 1). In 2016 and 2017, the OHSS frequencies were 1.3% and 1.2%, respectively. We found no significant change in the annual OHSS incidence rates (p = 0.17), and no trend for changes was observed in the annual incidence over the years (p = 0.24).

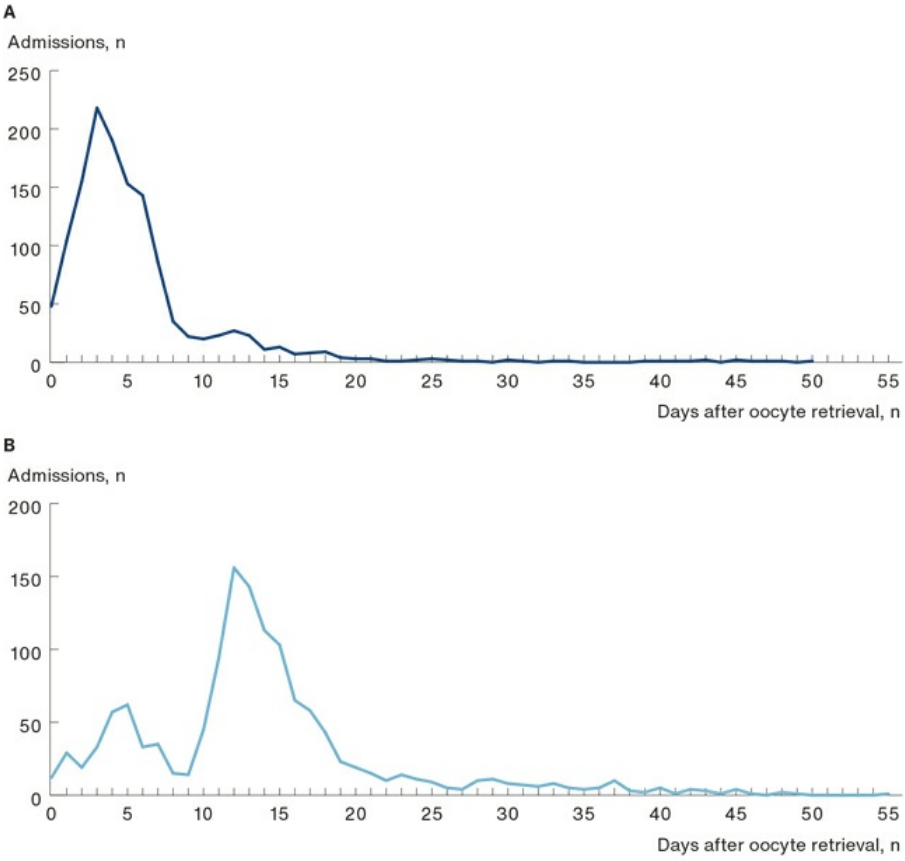
TABLE 1 Overall data of early and late ovarian hyperstimulation syndrome distributed over the years.

	Age, mean, yrs		IVF/ICSI-stimulated	Women with diagnosis of OHSS, n (%)			Cases of OHSS admitted to hospital for > 24h, n (%)		Time in hospital, mean, days	
Year	early OHSS[a]	late OHSS[b]	cycles, n	early OHSS[a]	late OHSS[b]	total	early OHSS[a]	late OHSS[b]	early OHSS[a]	late OHSS[b]
2001	32.5	31.0	8,805	46 (49.4)	47(50.5)	93 (1.1)	40 (87)	41 (87)	4.4	6.1
2002	31.2	32.3	9,630	42 (47.2)	47 (52.8)	89 (0.9)	35 (83)	40 (85)	5.1	6.0
2003	31.6	31.8	9,292	61 (48.4)	65 (51.6)	126 (1.4)	47 (77)	52 (80)	5.9	6.5
2004	31.7	31.6	9,598	54 (44.3)	68 (55.7)	122 (1.3)	44 (81)	58 (85)	4.3	8.5
2005	31.2	32.4	9,541	68 (50.4)	67 (49.6)	135 (1.4)	56 (82)	64 (96)	4.1	7.0
2006	32.2	30.7	9,936	57 (49.1)	59 (50.9)	116 (1.2)	44 (77)	48 (81)	5.8	7.3
2007	34.0	31.4	11,035	53 (42.8)	71 (57.3)	124 (1.1)	46 (87)	58 (82)	3.2	6.7
2008	31.6	32.2	10,478	54 (42.5)	73 (57.5)	127 (1.2)	41 (76)	52 (71)	4.4	7.8
2009	31.9	32.0	11,538	63 (46.3)	73 (53.7)	136 (1.2)	49 (78)	57 (78)	5.1	5.5
2010	31.7	32.1	12,234	81 (50.9)	78 (49.1)	159 (1.3)	67 (83)	59 (76)	4.2	5.8
2011	31.6	31.8	11,427	75 (52.4)	68 (47.5)	143 (1.2)	57 (76)	46 (68)	3.6	5.9
2012	31.3	32.6	11,707	63 (41.0)	91 (59.1)	154 (1.3)	44 (70)	62 (68)	3.9	5.4
2013	30.0	32.2	11,584	55 (42.0)	76 (58.0)	131 (1.1)	35 (64)	60 (79)	3.3	5.8
2014	32.1	31.6	11,670	80 (55.3)	65 (44.8)	145 (1.2)	54 (68)	51 (78)	3.6	5.4
2015	32.2	32.1	12,328	69 (45.7)	82 (54.3)	151 (1.2)	47 (68)	58 (71)	3.8	5.5
2016	32.4	33.0	12,689	90 (58.8)	63 (41.2)	153 (1.2)	61 (68)	35 (56)	3.3	5.2
2017	31.2	32.2	12,676	85 (54.1)	72 (45.9)	157 (1.2)	35 (58)	39 (77)	4.9	5.0
Total	31.8	31.9	186,168	1,096 (48.5)	1,165 (51.5)	2,261 (1.2)	842 (76)	868 (79)	4.3	6.2

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; OHSS = ovarian hyperstimulation syndrome.
a) Non-pregnancy-related.
b) Pregnancy-related.

In 170 (6.7%) women with an OHSS diagnosis, no oocyte retrieval was recorded prior to the OHSS admission. The distribution of the time of the diagnoses of early and late OHSS in relation to the number of days after oocyte retrieval (n = 2,098) are presented in **Figure 1**. Data in Figure 1 show the number of cases of early (non-pregnancy-related) and late (pregnancy-related) OHSS events diagnosed in relation to the number of days it was diagnosed after oocyte retrieval (n = 2,098). An abrupt rise in admissions occurred on day ten after retrieval, and the majority of late OHSS events were diagnosed within 19 days (Figure 1). Figure 1B shows that a minor share of women with pregnancy-related late OHSS presented with OHSS within nine days from oocyte retrieval. Figure 1B shows that the number of these women peaked at day five following retrieval. Such patients were only recorded once, and, as they achieved a pregnancy, they were classified as having late OHSS. After day 20 following oocyte retrieval, only a few new cases of OHSS were diagnosed.

FIGURE 1 Distribution of diagnosis of early (without a pregnancy) (**A**) and late (with a pregnancy) (**B**) ovarian hyperstimulation syndrome (OHSS) according to the number of days after oocyte retrieval (data are based on the 2,098 cycles with a preceding oocyte retrieval).



Among all women with a diagnosis of OHSS, 75% were hospitalised for more than 24 hours (Table 1). No difference was found in the proportion of women hospitalised for more than 24 hours due to early versus late OHSS (76% versus 77%, p = 0.56). However, women with late OHSS had a longer hospital stay (mean 6.3 days) than women with early OHSS (mean 4.2 days) (p < 0.001). **Figure 2** illustrates the number of days the OHSS patients spent in hospital. Overall, 77% of the women with OHSS were admitted to hospital for up to one week after their OHSS diagnosis (86% of the early and 69% of the late OHSS cases), 20% stayed in hospital for up to two weeks (14% of the early and 25% the late OHSS cases), whereas only 3% of all patients with OHSS stayed for more than two weeks (1% of the early and 6% of the late OHSS cases). Among all women with OHSS, the most common other complication was ovarian torsion, which occurred in 30 women (1.3%), thromboembolism occurred in four (< 1%) and ascites drainage was recorded in 250 women (11%).

A total of 123 women (10.9%) with late OHSS were recorded with miscarriage (9.8%) and ectopic pregnancies (1.1%) (**Table 2**). The overall prognosis for livebirth in women with late OHSS was 89%.

FIGURE 2 Number of days in hospital in women with early (—) and late (—) ovarian hyperstimulation syndrome.

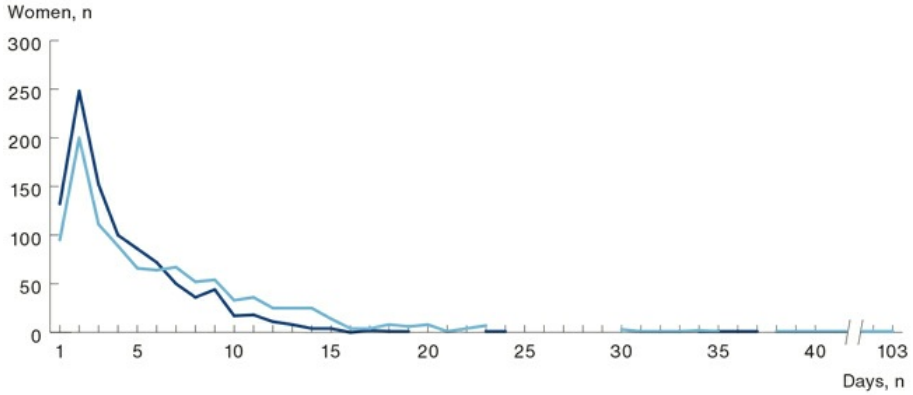


TABLE 2 Pregnancy outcomes of late ovarian hyperstimulation syndrome (OHSS).

Year	Late OHSS[a], n	Miscarriage, n	Ectopic pregnancy, n	Deliveries, n (%)	Induced abortion, n
2001	47	6	0	41	0
2002	47	4	1	42	0
2003	65	8	2	55	0
2004	68	9	0	59	0
2005	67	7	1	59	0
2006	59	2	1	56	0
2007	71	8	0	63	0
2008	73	6	2	62	3
2009	73	5	1	65	2
2010	78	7	0	70	1
2011	68	4	0	64	0
2012	91	8	2	81	0
2013	76	7	0	69	0
2014	65	6	2	56	1
2015	82	8	0	73	1
2016	63	7	0	54	2
2017	72	9	0	63	0
Total	1,165	111	12	1,032 (89)	10

a) Pregnancy-related.

DISCUSSION

Contrary to our anticipation, we found a stable frequency of both early and late OHSS over the past 17 years, with an overall annual incidence rate of 1.2% of stimulated ART cycles. This implies that recent developments, which

ought to have reduced the risk of OHSS, i.e. more frequent use of antagonist protocols, agonist triggering for patients at risk for OHSS, use of a freeze-all approach or individualised ovarian stimulation, have not been implemented sufficiently to reduce the National OHSS hospital admission rates in Denmark. Three main reasons may explain this observation. Either the four OHSS-preventive strategies stated above may a) not be used in practice as often as anticipated, b) not be used consistently or, c) may be less effective in reducing OHSS than expected when applied to the general population. Unfortunately, our large national data set collected over a 17-year period does not include detailed information about how individual cycles were handled in terms of the above-mentioned measures to reduce OHSS risk factors. Hence, the reasons for the lack of decline in OHSS remain speculative.

According to the latest European IVF monitoring European IVF-monitoring (EIM) Consortium report, the incidence of OHSS in Europe was only 0.3%, clearly lower than the 1.2% observed in the present study. However, these OHSS rates seem too low as the EIM calculated OHSS based on all cycles, including those with thawed embryos and even IVM and not only IVF/ICSI-stimulated cycles. Additionally, the number of ART cycles included in the denominator also comprised countries that did not report OHSS rates [13]. Despite high likelihood of underreporting in the EIM reports, the ESHRE data show the same tendency as the data in Denmark. Hence, from the first report that included OHSS rates in 2007 to 2014, the incidence of OHSS has remained overall constant in most of countries. Annual reports from Australia and New Zealand show OHSS rates from 0.73% in 2007 to 0.46% in 2016. OHSS included only women with hospitalisation and data were validated against hospital records by fertility centre staff, and, similar to our study, these data only included hospitalised women [14]. In the US, the Society for Assisted Reproductive Technology data from 2006 and 2014 reported an incidence of moderate to severe OHSS in about 1.2% of all ART treatments in 2006, declining to 0.5% in 2014 [15].

In comparison with the international data, OHSS rates in Denmark remain rather high. One reason may be that our rates were based on actual hospital admissions rather than on rates reported by ART doctors. The latter may lead to underreporting of the occurrence of OHSS, as shown in the United Kingdom, where the press (Daily Mail newspaper) pointed towards a substantial gap between the numbers of OHSS reported by the ART clinics to HFEA and the number of hospital admissions (1.6% of all stimulated cycles) in 2017. Subsequently, the HFEA performed a random single audition and reported that some cases were misreported. Estimation of the true OHSS incidence may be biased by misreporting (using erroneous denominators), misclassification of diagnoses (incorrect interpretation of symptoms by doctors) and underreporting (lack of time, bureaucratic coding systems). Based on the IVF-Worldwide Survey, it is estimated that, today, around 70% of all ovarian stimulation cycles for ART use the antagonist protocol [16]. We consider that the situation in Denmark is the same as in other countries. In the published meta-analysis comparing the long-agonist protocol versus the antagonist protocol, the distribution between early and late OHSS is unavailable, but according to the largest single study, the reduction in OHSS after the GnRH antagonist protocol occurred in terms of early as well as late OHSS [4-7]. In our study, neither early nor late OHSS was reduced. The GnRH-agonist triggering associated with a freeze-all policy in antagonist protocols prevented almost all cases of early and late OHSS, even though OHSS cases have occasionally been reported with this policy [17]. Even if Danish doctors have not implemented these two measures, we should have been able to see a reduction in OHSS rates owing to an expected higher use of the antagonist protocol.

In our study, we found that early OHSS saw a peak of hospital admissions four days after oocyte retrieval which then followed a declining trend until day ten (Figure 1). For pregnancy-related OHSS, the peak occurred 12 days after retrieval and then gradually declined (Figure 2). Overall, 1,710 women were hospitalised for more than 24 hours and they spent a mean number of 4.2 days (early OHSS) and 6.3 days (late OHSS) in a hospital bed (Table 1). The prognosis for live birth after late OHSS was 89% as the overall pregnancy loss rate was 12% (Table 2), which

is very similar to what has been found in earlier single-centre studies [18].

A limitation, but potentially also a benefit, of this study is that we have used hospital admissions for OHSS exclusively as a diagnosis criterion. However, most of our patients were admitted to hospital for more than 24 hours and stayed in the hospital for several days, indicating that they did have morbidity that demanded observation and treatment, although it remains unknown to which extent the duration of the hospital stay was influenced by other iatrogenic complications to ART, i.e. abdominal bleeding or infections. The ideal solution would have been to retrospectively validate all OHSS diagnoses by medical records, which was not done. Additionally, the classification of OHSS may have changed over time. However, according to the OHSS guideline of the Danish Fertility Society [19], the main reference during the period was Navot's classification from 1992 [20]. Overall, the number of possible misrecordings of OHSS has probably remained stable throughout the study period, so the finding that the overall risk of OHSS remained unchanged is likely valid. Finally, another limitation to the study is that details regarding individual characteristics like indication for treatment or BMI are unavailable. However, a main risk factor for OHSS is young female age and, as seen in Table 1, age remained constant across the study period.

In Denmark as well as in other European countries, OHSS remains a severe iatrogenic risk related to ART that still needs to be addressed. Greater focus should be placed on correct diagnostics of patients admitted to hospital after ovarian stimulation as most of these patients are diagnosed with OHSS even though they have a wide range of other conditions. This is partly due to the poorly defined OHSS criteria where international consensus on more clinically relevant and feasible OHSS criteria is highly needed.

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