

Severe ovarian hyperstimulation syndrome with GnRH agonist trigger during the COVID pandemic: lessons learned from an unusual case

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Received date: April 16, 2021; Accepted date: April 21, 2021; Published date: April 30 2021

Citation: Schrader E. , Hurley T. , Welch D. , Ying Y. , Eskew A. , Bradley S Hurst* (2021) Severe ovarian hyperstimulation syndrome with GnRH agonist trigger during the COVID pandemic: lessons learned from an unusual case. *J.Obstetrics Gynecology and Reproductive Sciences*. 5(4): DOI: [10.31579/2578-8965/070](https://doi.org/10.31579/2578-8965/070)

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Abstract:

Background: Injectable gonadotropins stimulate multi-follicular recruitment and allows retrieval of multiple oocytes for assisted reproduction. The widespread utilization of gonadotropin releasing hormone agonist (GnRHa) to induce oocyte maturation for oocyte retrieval has nearly eliminated the risk of severe ovarian hyperstimulation syndrome (OHSS), and only a few cases have been reported in the literature. The rarity of severe OHSS may lead to the mistaken conclusion that gonadotropin stimulation can be safely administered with limited monitoring, even in high-risk patients. We present an unusual case of a woman with limited monitoring due to the COVID pandemic who developed severe OHSS before GnRH agonist trigger and oocyte.

Case Presentation: A 29-year-old nulliparous woman with polycystic ovarian syndrome (PCOS) initiated ovarian stimulation for oocyte retrieval. She had a robust initial response, and developed worsening abdominal pain, bloating, nausea, vomiting, and decreased appetite before retrieval. GnRH agonist was given to "trigger ovulation and retrieval scheduled due to the low reported incidence of severe OHSS. Symptoms progressed, and on the morning of retrieval, ultrasound demonstrated bilaterally enlarged ovaries >10cm and 48 oocytes were retrieved for a planned cryo-all cycle. She was hospitalized on the day of retrieval for severe OHSS and had two large-volume paracenteses. She was stable and discharged home by day 5, and symptoms markedly improved with the onset of menses. She has an ongoing pregnancy from her first frozen embryo transfer.

Conclusion: We add a rare case of severe OHSS with a GnRHa trigger and cryo-all protocol with the onset of symptoms before GnRH agonist administration. Although rare, severe OHSS may still occur with a GnRHa trigger, and caution is needed when an initial robust response is identified. Here we also provide an opportunity to review the important patient risk factors for the development of OHSS and measures to reduce the risk in excessive responders.

Key Words: ovarian hyperstimulation syndrome; fertilization in vitro; leuprolide trigger; polycystic ovarian syndrome; assisted reproduction technologies; controlled ovarian stimulation; COVID-19

Introduction:

Ovarian stimulation with supraphysiologic levels of gonadotropins allows retrieval of multiple oocytes for assisted reproduction procedures. However, controlled ovarian stimulation (COH) poses risk for ovarian hyperstimulation syndrome (OHSS), one of the most common and severe iatrogenic complications of COH.

During follicle growth, rapid perifollicular neovascularization occurs. In the past, human chorionic gonadotropin (hCG) was almost universally used to trigger follicular and oocyte maturation for oocyte retrievals. HCG administration is problematic, however, for extremely hyperstimulated

ovaries and may result in OHSS. Exogenous hCG causes follicle luteinization, which substantially increases vasoactive substance production [1]. Luteinization upregulates the VEGF receptor on ovarian endothelial tissue, a primary factor for increasing vascular permeability.

Mild ovarian enlargement with the growth of multiple follicles is typical during COH [2], but the overproduction of vasoactive substances is largely due to the introduction of the hCG trigger. With hCG trigger administration after ovarian hyperstimulation, one study reported a 3 to 6% incidence of moderate OHSS and a up to a 2% incidence of severe OHSS [3]. The World Health Organization estimates the incidence of severe OHSS to be 0.2 to 1% of all stimulation cycles [4].

Severe OHSS can result in third spacing and lead to ascites, dyspnea, hemoconcentration, electrolyte abnormalities, diminished renal perfusion, potential end organ damage, and thromboembolism [5]. The third spacing of fluid can result in a large-volume ascites in the peritoneal cavity, with potential for moving to the thorax and causing hydrothorax and pleural effusions. The combination of ascites and significantly enlarged ovaries leads to extreme abdominal pain, dyspnea, bloating, physical distension, nausea, vomiting, and diarrhea. Severe cases warrant hospitalization for symptom control.

Risk factors for OHSS have been identified both before and during ovarian stimulation. Patients at high risk of OHSS include women with PCOS, elevated antimüllerian hormone (AMH) > 3.3ng/mL and a high antral follicle count [6]. One study found that women with an AMH level >10ng/mL were at greater than a 3-fold increased risk of developing OHSS [7]. Risk factors during stimulation include many growing

follicles, a marked elevation of estradiol, or rapidly increasing estradiol levels (8). When estradiol levels reach 6000ng/mL during stimulation, one study reported 38% of patients who developed OHSS when hCG trigger was administered [9]. Another study found an increased incidence of OHSS with increasing number of oocytes retrieved [9]. Additionally, PCOS (3,8), and prior history of OHSS had a higher risk of OHSS (3). Women who become pregnant in a fresh cycle have a higher risk of late OHSS due to the natural and increasing production of hCG during the first trimester [10].

Utilization of GnRH-agonists such as leuprolide to induce oocyte maturation before retrieval has mitigated the risk of severe OHSS (1). Studies comparing GnRH to hCG have found no cases of OHSS with GnRH trigger compared to hCG administration [11-14], but a few cases of severe OHSS have been reported (Table 1).

Case	Age	Peak estradiol	# of antral follicles	# of Follicles retrieved	Severity of OHSS	Pregnancy immediately following?	Source
1 ¹	25	N/A	N/A	30	Severe	Yes	(17)
2	29	4300 pg/mL	25	30	Severe	No	(18)
3	27	3578 pg/mL	N/A	30	Severe	No	(18)
4	27	5985 pg/mL	40	27	Severe	No	(19)
5	30	6041 pg/mL	40	45	Severe	No	(19)
6	31	10,904 pg/mL	38	35	Severe	No	(19)
7 ²	30	13,041pg/mL	N/A	13	Severe	No	(20)
8 ¹	36	14,533 pg/mL	N/A	36	Severe	Yes	(21)
9	32	N/A	N/A	41	Severe	No	(22)

¹Cases that resulted in intrauterine pregnancy immediately after ovarian stimulation and egg retrieval

²One case was disputed as possibly secondary to hemorrhage

Table 1: Summary of reported cases of OHSS with GnRH trigger protocols.

In this case report, we add another rare case of severe OHSS in a patient who underwent GnRH trigger therapy and discuss measures to minimize future risk. Since 2017, we have performed 1200 oocyte retrievals at our center, including 371 retrievals after GnRH agonist trigger. During COVID, we limited monitoring to visits considered “essential,” eliminating routine ultrasound and estradiol on stimulation day 6 to minimize office visits and the potential for exposure, according to Atrium Healthcare System and Centers for Diseases Control guidelines.

Methods:

Case Report

This 29-year-old nulliparous woman with BMI of 30 met clinical criteria for PCOS based on elevated testosterone 160 ng/mL, hirsutism, polycystic ovarian morphology on ultrasound, oligomenorrhea, and a 3-year history of infertility. Tubal patency was confirmed by hysterosalpingogram and uterine assessment by sonohysterogram was normal. Thyroid stimulating hormone (TSH) was 2.7ng/mL, and she was prescribed levothyroxine 25mcg. Prolactin, hemoglobin A1C, and vitamin D were normal. AMH was 21.9ng/mL, cycle day 3 FSH 4.9 and estradiol 34 pg/mL.

She initiated oral contraceptives the cycle immediately before the stimulation cycle, then stopped and began ovarian stimulation with 225U of rFSH (Gonal-F) for 3 days. The “day 4” estradiol was 1066 pg/mL, and she initiated human menotropin (HMG) 75 units daily and the dose of rFSH reduced to 150 units daily. Due to modified protocols during the COVID-19 pandemic to limit the number of required visits, 0.25mg GnRH antagonist (Cetrotide) was started on stimulation day 6, and with the understanding that the risk of severe OHSS with a GnRH agonist trigger was rare, no additional monitoring was performed until cycle day 8, when estradiol was 7734 pg/mL and over 40 follicles measuring < 10mm were identified, including lead follicles 15mm and 12.5mm. Stimulation was continued and on day 11, estradiol was 10,4000 pg/mL and 30 follicles measuring > 10 mm, more than 40 < 10mm, but only 1 measured 18mm. Minimal free fluid was noted at this time. Leuprolide 40mg was administered the following day without ultrasound to limit monitoring. LH was 17.7 and progesterone 56.1 the day after trigger.

On the day before the GnRH agonist trigger, she began experiencing bloating, abdominal pain with movement, and decreased appetite. Her symptoms progressed until the day of her retrieval, where she experienced progressive shortness of breath attributed to abdominal distention. At presentation for retrieval, she required 1L O2 via nasal cannula and was

tachycardic to 117. During retrieval, the ovaries were over 10cm in diameter and there was a large volume of free fluid. Nearly half of the follicles were unable to be aspirated due to access issues related to the significant ovarian enlargement. 750mL of blood-tinged ascites fluid was removed transvaginally at the completion of egg retrieval. 42 oocytes were retrieved, 29 fertilized with conventional insemination, and 11 blastocyst embryos were cryopreserved.

The patient was admitted and underwent aggressive fluid resuscitation, and was started on cabergoline, aspirin, and daily GnRH antagonist. Lovenox and sequential compression devices were started for VTE (venous thromboembolism) prophylaxis. Admission laboratory results showed an elevated creatinine 1.15 mg/dl (baseline 0.85 mg/dl), hemoglobin 12.4 g/dl, hematocrit 22%, platelets 168 and INR of 1.1. COVID-19 PCR tests were repeatedly negative. Her weight on admission was 84kg; by hospital day 3, she had gained 10kg. A second paracentesis was performed on hospital day 3 due to worsening dyspnea and inability to tolerate oral intake, and 1.7 L of fluid was obtained. Afterwards she improved. She was discharged on hospital day six and began her period 7 days after retrieval and quickly returned to baseline weight.

She continued to experience dyspnea and was admitted two weeks later for treatment of pneumonia. COVID-19 testing continued to be negative. Symptom eventually resolved. Frozen embryo transfer was performed in a programmed cycle approximately 3 months after retrieval, and she has a normal ongoing pregnancy.

Discussion:

The use of a GnRH agonist to trigger oocyte maturation has been an important development to reduce risk of ovarian hyperstimulation syndrome. It has previously been postulated that the use of GnRH agonist triggers can completely avoid OHSS risk for patients [11] and a Cochrane Review of 17 RCTs cited no cases of OHSS associated with an exclusively GnRH-triggered follicular maturation, which solidifies the safety of GnRH agonist trigger protocols [15]. However, since publication in 2014, a few cases of OHSS after GnRH trigger protocol have been reported (Table I) [16-22]. A total of nine cases are detailed in Table 1. However, three of these can be reasonably excluded as two were exacerbated by pregnancy in fresh embryo transfer cycles and another had suspected hemoperitoneum secondary to post-procedural hemorrhage, hypothetically mimicking OHSS symptomatology. A recent review concluded that OHSS is eliminated when no luteal support is administered [22]. In our case report, we present a case of OHSS coming from a GnRH-agonist trigger and cryopreservation of all embryos in the absence of endogenous or exogenous hCG.

This case is particularly interesting as the patient reported the onset of her symptoms (abdominal pain and bloating, nausea, and abdominal distension secondary to abdominopelvic ascites) before GnRH agonist trigger. At this point, her estradiol level had surpassed 10,400 pg/mL. Her presentation suggests an exaggerated response to the GnRH antagonist protocol that preceded her trigger, and thus, the development of OHSS without any administration of follicular maturation drugs. Literature review for similar such cases is scant and lacks content revealing the development of OHSS without an ovulation trigger.

The administration of a follicular maturation trigger, whether that be hCG or GnRH agonist, has been a requirement for all reported cases of OHSS thus far. This trigger is thought to be the factor leading to mass activation of VEGF and other inflammatory markers, but this case reveals the potential for developing OHSS during GnRH antagonist protocol without any administration of trigger. This case exposes a research gap in the foundational explanation for how this occurred.

Furthermore, this case poses the question: how could this have been prevented and what guidelines need to be established to avoid this

outcome in the future? While difficult to predict exactly which patients will develop OHSS, prevention starts with identification of each patient's risk factors and subsequent protocol modification to individualize each patient's treatment. Our patient's risk factors included a BMI 30, PCOS, and an AMH of 21.9 ng/mL. Furthermore, an exaggerated response to the GnRH antagonist protocol was first suspected on stimulation day 4, with a significantly elevated estradiol level of over 10,400pg/mL. We now reduce the stimulation dose for patients who have a markedly elevated estradiol after 3 days of ovarian stimulation. However, there is little to guide the day 4 estradiol level that would require a dose reduction, but 1,000 ng/mL is too high!

One small observational study published in 2019 expanded upon the GnRH trigger protocol in patients at critically high risk of OHSS and report good outcomes (16). In this study, two GnRH agonist triggers were administered, the second 12 hours after the initial, and GnRH antagonist was used for the three days after oocyte retrieval. The authors identified "high risk" as greater than 30 oocytes at retrieval with peak estradiol levels > 10,000 pg/mL. Our reported case meets those criteria and from this study, potentially could have benefited from this protocol adjustment. The American Society for Reproductive Medicine's practice bulletin on OHSS also supports a similar set of various factors that providers can look out for in their patients, like PCOS, elevated AMH levels, peak estradiol levels, and high oocyte counts on retrieval [5]. These resources suggest that there is still an opportunity for advancing what's no considered standard ovarian stimulation as well as the parameters around which we monitor these patients to eliminate the rare but serious development of OHSS.

Conclusion:

In summary, this case adds a rare case of OHSS with GnRH agonist trigger and cryopreservation of all embryos without luteal support. Risk factors included an extremely high AMH and extremely rapid initial response to gonadotropin stimulation. It is likely that OHSS might have been less severe if the initial stimulation dose was reduced, or if the dose had been reduced on stimulation day 4. We expose a research gap warranting further investigation into the mechanisms responsible for causing OHSS, and mechanisms, policies, and protocols to reduce the risk.

Conflict of Interest Statement:

Authors declare there are no conflicts of interest associated with this manuscript.

Patient Consent:

This manuscript was deemed exempt from our Carolinas Medical Center Institutional Review Board.

Financial Disclaimer:

None.

Author Contributions:

All authors were substantially involved in the acquisition of case report data, contributing to drafting of the manuscript, and critically revising the manuscript for important intellectual content.

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