Iatrogenic Ovarian Hyperstimulation Syndrome in Late Luteal Phase – A Rare Case Report

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Abstract: Ovarian hyperstimulation syndrome is an iatrogenic medical complication unique to stimulatory infertility treatment. Characteristics of the syndrome include cystic ovarian enlargement, increased capillary permeability resulting in extravascular fluid accumulation, and intravascular volume depletion. It is a self-limiting disease in mild cases but can cause renal failure, hydrothorax, and respiratory distress that can cause mortality in severe cases. In this case, we aimed to report moderate ovarian hyperstimulation (grade 3) syndrome, ultimately resulting in ovarian torsion and salpingooophorectomy. Case presentation-A 29-year-old female known case of polycystic ovarian syndrome underwent ovulation induction 22 days later. She presented to our hospital with severe abdominal pain, abdominal distension, and vomiting. She was admitted and diagnosed with Grade 3 Ovarian hyperstimulation syndrome medical management, given the patient got better symptomatically. 10 days later, she presented in casualty with abdominal pain and was diagnosed with right ovarian torsion and right salpingooophorectomy done. Conclusion: We should rule out risk factors for ovarian Hyperstimulation syndrome before treating any infertility patient. Patients with ovarian hyperstimulation syndrome must be identified early and referred urgently to a tertiary care hospital. Ovarian hyperstimulation syndrome can result in serious morbidity and mortality if left untreated.

Keywords: polycystic ovarian syndrome, ovarian torsion, ovulation induction, Hyperstimulation, Secondary Infertility.
1. INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS)\(^1\) is a life-threatening clinical complication that manifests as massive ovarian enlargement. Most common iatrogenic cause following ovulation induction or ovarian hyperstimulation. Ovulation induction is done by various drugs like oral drugs like Letrozole, clomiphene citrate, Tamoxifen, injectables like gonadotropins (urinary), Recombinant gonadotropin analogs like agonists and antagonists, etc.; among these, Letrozole is the least common to cause hyperstimulation. The hypothalamus-pituitary-ovarian function decides the choice of medications for ovulation induction. If the hypothalamus is adequate oral regimen is preferred. If there is any dysfunction in the hypothalamus, injectable gonadotropin is preferred. Three different protocols for administering gonadotropins, like the step-up protocol in which 75IU is starting dose, and 75IU increases every 7 days until the follicles are recruited\(^2\). Low dose step-up in which 37.5IU - 75IU is starting dose + 37.5IU increase every 7-14 days if follicles are not recruited\(^3,4\). Step-down protocol in which 150IU until the dominant follicle is more than 10mm, then 112.5 IU for 5 days, and 75IU for 5 days until ovulation. Clomiphene citrate is known to cause hyperstimulation syndrome if used at more than 200mg daily. Gonadotropins have a high chance of developing hyperstimulation. Patients with clinical conditions like polycystic ovarian syndrome, young age, lower body mass index (BMI), previous history of ovarian hyperstimulation syndrome, and genetic predisposition have a higher chance of developing hyperstimulation. Biochemical indices like plasma estradiol, Insulin resistance, Anti Mullerian hormone (AMH), and follicular stimulation hormone (FSH) help predict hyperstimulation. Ultrasound indices like Polycystic ovarian pattern, High antral follicular count, and ovarian volume also help predict hyperstimulation. Incidence of moderate or severe OHSS 3% to 8%\(^5\). Symptoms vary from abdominal discomfort, nausea, vomiting, abdominal distension, pain in the abdomen, decreased urine output, dyspnea, pleural effusion, electrolytes imbalance, and an increased tendency for thromboembolism due to an increase in permeability of capillaries leading to fluid leakage from peritoneal and ovarian surfaces due to ovarian stimulation. It is a rare iatrogenic complication of ovarian stimulation during the luteal phase\(^6,7\).

2. CASE REPORT

29 years old P1L1 woman came to the OPD of Gynecology with severe abdominal pain, vomiting, and mild abdominal discomfort. Her PR- 98/min, BP – 110/60 mmHg, SPO2 98% (room air), and RR – 20/min. The physical examination showed a palpable tender mass occupying the hypogastric region, right and left iliac fossa corresponding to 16 weeks' gravid uterine size. There is no evidence of ascites or lung signs. She attained menarche at 13 years of age and had regular cycles. She conceived spontaneously 6 years back on first conception, delivered by normal vaginal delivery with no complications during delivery. The patient was on treatment for secondary infertility, for which she took one cycle of Letrozole followed by a second cycle of Clomiphene Citrate 100mg from day 3 to 7. After 22 days, she developed severe abdominal pain associated with vomiting. She went to a nearby hospital, was treated with analgesics, and was referred to our hospital.

2.1. Investigations

Laboratory tests showed a Complete hemogram, serum electrolytes, urea, and creatinine are in the normal range. Abdominal and transvaginal USG (figure 1) showed uterus-8.1\(\times\)5.2 \(\times\) 4.1cm, endometrial thickness of 8.6mm. The right ovary appears enlarged- 12.3\(\times\)7.3cm & Left ovary appears enlarged- 9.8\(\times\)7.5cm. Bilateral ovaries appear enlarged and show multiple cysts of varying sizes; few cysts show hemorrhagic content. Minimal free fluid was noted in the peritoneal cavity. No evidence of pleural effusion.
Grade 3 OHSS was diagnosed based on the history of infertility treatment, enlarged ovaries (12.3× 7.3cm), and ultrasound evidence of ascites. She was given symptomatic management with close monitoring. Daily vitals monitoring with abdominal girth measurement, lung signs, and urine output. Advised fluid restriction. Medical management with Cabergoline 0.5mg for 10 days, injection of Cetrorelix 0.25mg for 5 days, and injection of Enoxaparin 0.4mg for 5 days. Prognosis Patient improved symptomatically and hence discharged at request. 10 days later, again, she presented with severe abdominal pain and was diagnosed with right ovarian torsion and right Salphingo oophorectomy. Histopathology revealed a normal fallopian tube and an infarcted surface with a viable focal lining in the ovary.
3. DISCUSSION

Ovarian hyperstimulation syndrome (OHSS) is characterized by multi-follicular development and ovarian enlargement. It is an iatrogenic complication of ovulation induction. It usually occurs with gonadotropin therapy and rarely with clomiphene citrate. A variety of chemical mediators like cytokines, vascular epidermal growth factor, and tumor necrosis factor is thought to be stimulated due to human chorionic gonadotropin that leads to an increase in permeability of vessels and fluid accumulation in extravascular spaces in OHSS. Two patterns of OHSS onset have been described in Table 1. The proposed RCOG classification based on the severity of OHSS symptoms is given in Table 2. Table 3 represents the medical management of different grades of OHSS.

<table>
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<th>Table 1: Patterns of OHSS onset</th>
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<td>Early onset    3-7 days following the trigger</td>
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<td>Late-onset    12-17 days after the trigger</td>
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<th>Table 2: Classification based on the severity of symptoms</th>
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<td>RCOG</td>
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<tr>
<td>Mild</td>
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<td>Grade 2</td>
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<td>Moderate</td>
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Fig 3: Histopathology Pictures A & B
In most cases, OHSS disappears spontaneously after 6-8 weeks. Rarely it may turn fatal in patients who are having pleural effusion or pericardial effusion, hypovolemia. The main treatment of OHSS is symptomatic and supportive. During the follow-up of the patients, Hemoglobin, hematocrit, electrolytes, renal function tests, and liver function tests are to be done. Surgical management is indicated only in cases of ovarian torsion or ovarian rupture.

4. EPIDEMIOLOGY AND RISK FACTORS

Incidence is different for different regimens used. Both urinary or recombinant Gonadotropins have a higher incidence. The incidence of moderate or severe OHSS is 8% in patients induced by clomiphene citrate. 2% of all IVF cycles will have OHSS. Patients with PCOS have a higher risk of developing hyperstimulation. If the number of follicles retrieved after ovulation induction is more than 14 risk of developing ovarian hyperstimulation syndrome increases. Younger patients, and women with low BMI, have a high risk of developing hyperstimulation. Pregnancy increases the risk of developing hyperstimulation and prolongs the symptoms’ duration.

5. CONCLUSION

Before treating infertility with ovarian stimulation drugs like clomiphene citrate and gonadotropin, physicians should evaluate the patient carefully to rule out risk factors like PCOS and young age, thereby preventing OHSS. The patient with OHSS should be identified early and treated urgently. If left untreated, it can result in serious complications.

6. COMPLIANCE WITH ETHICAL REQUIREMENTS

We declare that this article is original, not submitted for publication anywhere else, and was not published anywhere previously. Written and informed Consent was taken from the patient for publishing the article. Dr. Nithya Dr. Nitya operated on the case. All authors read and approved the final manuscript.

7. AUTHORS CONTRIBUTIONS STATEMENT

Conflict of interest declared none.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES


