Complications of Intrauterine Insemination

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ABSTRACT

Intrauterine insemination (IUI), a commonly performed procedure in the treatment of infertility, is one of the easiest and safe procedures as it is the least invasive method for assisted reproduction. In most women, complications of IUI are rare; however, they can sometimes occur, which may be directly or indirectly related to the procedure. These could be due to ovarian stimulation like ovarian hyperstimulation syndrome (OHSS), multiple pregnancies or due to the insemination procedure like pain, infections, trauma and bleeding, etc. Other complications that may rarely occur include abortion, ectopic pregnancy and accidental insemination with the wrong sample. Of these, OHSS is an iatrogenic and one of the most dreaded complications associated with ovarian stimulation. It is associated with a wide-spectrum of clinical signs and symptoms, ovarian enlargement, fluid shift from intravascular to extravascular compartment and changes in biochemical parameters.

Keywords: Intrauterine insemination, infertility, complications, OHSS

Intrauterine insemination (IUI) is one of the easiest and safe procedures as it is the least invasive method for assisted reproduction. Still, complications can sometimes occur, which may be directly or indirectly related to the procedure. The treating physician should have a complete knowledge and understanding of these complications to minimize their incidence and also should be capable of treating them in case they occur. The complications can be divided as:

- Due to ovarian stimulation
- Due to insemination procedure
- Other complications.

COMPLICATIONS DUE TO OVARIAN STIMULATION

IUI is usually combined with controlled ovarian stimulation and natural cycle IUI is rare. Controlled ovarian stimulation (COS) can be associated with certain complications, which can be divided into immediate and delayed: *Immediate*: Ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies; *Delayed*: Risk of ovarian cancer.

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Ovarian Hyperstimulation Syndrome

OHSS is an iatrogenic and one of the most dreaded complications associated with ovarian stimulation. It is associated with a wide-spectrum of clinical signs and symptoms, ovarian enlargement, fluid shift from intravascular to extravascular compartment and changes in biochemical parameters. It is usually seen after stimulation with gonadotropins; however, can rarely occur after clomiphene citrate use.

Incidence

The incidence of OHSS ranges from 3% to 23% and varies according to the ovulation induction protocols and the risk profile of population being studied.[1] The incidence of mild, moderate and severe of OHSS is 8-23%, 0.005-7% and 0.008-2%, respectively.

Pathophysiology

The exact pathophysiology is still not elucidated. The major events are neovascularization and increased vascular permeability that lead to acute fluid shift from the intravascular to extravascular compartment. This shift occurs due to release of vasoactive substances from the ovary under the influence of human chorionic gonadotropin (hCG). These are renin-angiotensin, interleukins, nitric oxide and vascular endothelial growth factor (VEGF).[2] It has recently been identified that increased sensitivity of the follicle-stimulating hormone (FSH) receptor to hCG is responsible for spontaneous OHSS occurring during pregnancy.[3]

Classification of OHSS

OHSS has been classified into various stages and grades according to the clinical symptoms, signs, ultrasonographic findings and laboratory parameters. The most commonly used is the Golan's classification which has divided it in 3 stages: mild, moderate and severe and 5 grades (Table 1).[4] The severest grade of OHSS is further classified by Navot as severe and critical life-threatening depending on clinical and biochemical findings to indicate when management in an intensive care setting should be considered (Table 2).[5]

The purpose of clinical staging is to guide patient management. In general, mild and moderate forms of OHSS can be treated expectantly in the outpatient department (OPD). Those with severe form should be admitted and those with critical OHSS are best managed in consultation with other specialists in intensive care setting.

Complications of OHSS

- Vascular complications: Venous compression, immobility and state of hypercoagulability can cause deep vein thrombosis. Cerebrovascular complications can occur secondary to these thromboembolic events.
- Liver dysfunction
- Renal dysfunction
- Respiratory compromise
- Adnexal torsion, rupture or hemorrhage.

Table 1. Golan's Classification of OHSS[4]

Grade I: *Mild* - Abdominal discomfort/distension

Grade II: *Mild* - Features of Grade I along with nausea, vomiting and/or diarrhea, ovaries enlarged 5-12 cm

Grade III: *Moderate* - Features of mild OHSS and USG e/o ascites

Grade IV: *Severe* - Features of moderate OHSS *plus* clinical e/o ascites and/or hydrothorax with/or difficulty in breathing

Grade V: *Severe* - All of the above *plus* changes in blood volume, increased blood viscosity due to hemoconcentration, coagulation disturbances and diminished renal perfusion and function

Table 2. Clinical Signs and Laboratory Criteria of OHSS[5]

	Mild-to-moderate	Severe	Critical
Ovarian enlargement	5-12 cm	>12 cm	Variable
Abdominal distension	Moderate	Severe	Tense
Clinical ascites	None	Yes	Tense
Hydrothorax	None	Possible	Yes
Pericardial effusion	None	Infrequent	Infrequent
Decreased renal function	None	Infrequent	Frequent
Renal failure	None	None	Possible
Thromboembolism	None	None	Possible
ARDS	None	None	Possible
Hemoconcentration	<45%	45-55%	>55%
WBC count	<15,000	15-25,000	>25,000
Liver enzymes	Normal	Elevated	Elevated
Creatinine (ng/mL)	<1.0	1-1.5	>1.6
Creatinine clearance (mL/min)	>100	50-100	<50

ARDS = Acute respiratory distress syndrome; WBC = White blood cell.

Prediction

Various factors have been identified to help define patients at high risk for OHSS (Table 3). All patients undergoing ovulation induction should be closely monitored with:

- **Ultrasound follicular monitoring:** All follicles including the smaller ones should be measured. The small (<9 mm) and intermediate follicles are more dangerous as these continue to grow and produce estradiol following hCG administration.[6]

  Patients with polycystic ovary syndrome (PCOS) are more likely to develop OHSS than those without polycystic ovaries as these have high sensitivity to gonadotropin stimulation due to large cohort of FSH sensitive small antral follicles.[7]
- **Serum estradiol levels:** A high level and a steep rise can predict likelihood of developing OHSS.

Prevention

- **Withholding hCG:** hCG trigger is usually given when the follicles reach 16-25 mm in size and estradiol level reaches 200-400 pg/mL per leading follicle. hCG is withheld in an IUI stimulated cycle if serum estradiol levels are more than 1,500 pg/mL. USG findings of more than 6 leading follicles can also be used as a criterion to withhold hCG.

  Also, if estradiol levels are more than doubling during 2-3 days (steep slope) then it should be regarded as a serious warning sign and hCG should be withheld in that cycle. When hCG is withheld:
  - Follicles can be aspirated and embryos cryopreserved
  - Continue GnRH agonists after stopping gonadotropins. Once down regulation occurs, cycle can be restarted at a lower dosage.
- **Delaying hCG (coasting):** When estradiol levels are high, hCG is withheld, gonadotropin-releasing hormone (GnRH) agonist is continued and gonadotropins are stopped till estradiol (E2) falls, following which hCG is given.[8] Withholding hCG causes apoptosis of granulosa cells and atresia of large number of follicles. Long coasting periods; however, have a negative impact on number of oocytes, implantation and pregnancy rates.[9,10]
- **Decreasing dose of hCG:** Lower dose of hCG (5,000 units instead of 10,000) may avoid hyperstimulation by exerting shorter periods of stimulation.
- **Use of GnRH agonist instead of hCG for luteinizing hormone (LH) surge:** As period of stimulation is lesser with GnRH agonist surge, there is no hyperstimulation. The rates of fertilization, implantation, clinical pregnancy, ongoing pregnancy and abortion rates observed are similar to hCG.[11]
- **Follicle aspiration:** Follicle aspiration can decrease the chance of OHSS.[12] However, some studies contradict this.
- **Albumin/hydroxyethyl starch:** This increases the serum oncotic pressure and prevents leakage of fluid in the third space. This is used as a prophylactic measure. The disadvantage is that its oncotic action lasts only for 36 hours.
- **Conversion to an *in vitro* fertilization (IVF) cycle, cryopreservation of embryos** and subsequent transfer in a later cycle. This helps decrease the chances of OHSS with the advantage of not losing the cycle and replacing the frozen thawed embryos in a later cycle.
- **Steroids:** Methyl prednisolone has been tried in cases of OHSS.[13]
- **Cabergoline:** This dopamine receptor agonist inactivates VEGF receptor and prevents increased vascular permeability. It is administered in a dose of 0.5 mg/day, starting from the day of hCG, for 8 days. The incidence of OHSS is significantly reduced.[14]

Table 3. Risk Factors for OHSS

Predicting factors	High risk	Low risk
Age	<35	>36
PCOS	Present	Absent
Build	Lean, thin	Heavy
No. of follicles	Multiple	Few
History of OHSS	Present	Absent
Induction protocol	GnRH agonist	CC or hMG
Luteal supplementation	Yes	No
Outcome	Pregnant	Not pregnant

OHSS = Ovarian hyperstimulation syndrome; PCOS = Polycystic ovary syndrome; GnRH = Gonadotropin-releasing hormone; CC = Clomiphene citrate; hMG = Human menopausal gonadotropin.

Treatment

The condition is self-limiting and usually resolves in 10-14 days. The treatment depends on the severity of the disease. The investigations and monitoring of OHSS patients is summarized in Table 4.

Table 4. Investigations and Monitoring of OHSS Patients

General condition: Regular charting of

- Vital signs: Pulse rate, respiratory rate, temperature
- Weight chart
- Abdominal girth
- Input-output record

Biochemical tests:

- Hematocrit
- Serum electrolytes
- Liver function tests
- Renal function tests
- Coagulation profile
- Blood gases and acid base balance
- Serum β-hCG

Ultrasonographic examination

- Ovarian size
- Amount of ascites
- Presence of hydrothorax
- Pregnancy: Single/multiple

Mild OHSS/Grade I

The treatment is usually conservative and is done on an outpatient basis with a close follow-up. One should reassure the patient. She should be advised to have plenty of fluids and to avoid exertion.

Grade II

Minimize physical activity and take plenty of fluids. Analgesics and antiemetics may be used as required. Serum hematocrit and electrolytes should be monitored. Input-output record should be maintained. Reassessment is required if there is increase in weight of more than 2 kg or if there is worsening of symptoms.

Indication of hospitalization

- Grade II or III OHSS if:
  - Intolerable nausea or vomiting
  - Hypotension
  - Pleural effusion
  - Ascites
  - Hematocrit >48%
  - Sodium <135 mg/L
  - Potassium level >5.0 mg/L
  - Serum creatinine >1.2 mg.
- All cases of Grade IV or V.

Aim

- Correction of circulatory volume
- Correction of electrolyte imbalance
- Maintaining renal function
- Prevention of thrombosis.

Maintaining intravascular volume: As there is hyponatremia, normal saline with or without glucose is the main crystalloid used. Plasma expanders like albumin are also used as there is protein loss in the third space. Other fluids like mannitol, dextran and fresh frozen plasmas can also be used.

Prevention of thrombosis: Low dose heparin can be used in cases where there is altered coagulation profile. Thromboembolic events require therapeutic anticoagulation with heparin.

Diuretics: These are used if oliguria persists in spite of restoring intravascular volume or in case of pulmonary edema. If renal failure still does not resolve with these measures, dopamine is added to dilate the renal vasculature.

Ascites: Paracentesis is done if there is severe discomfort, venous return is compromised, respiratory distress, renal compromise or hemoconcentration unresponsive to medical therapy. It should only be done if patient is hemodynamically stable.

Paracentesis of hydrothorax: This is done in cases of pleural effusion leading to dyspnea. Severe respiratory compromise may require ventilatory support.

Termination of pregnancy: If critical condition still doesn't improve, one may consider termination of pregnancy.

Laparotomy is required in cases of ovarian torsion, hemorrhage and rupture.

Multiple Pregnancies

This is an inevitable complication associated with ovarian stimulation. This is increased more when gonadotropins are used for ovarian stimulation compared to clomiphene citrate. It is very important to carefully monitor the patients undergoing COS *plus* IUI to minimize the incidence of multiple pregnancies. These births are associated with significant maternal morbidity and also preterm birth with its sequel of neonatal mortality and morbidity.

Women at high risk of multiple pregnancies are usually less than 30 years of age; with 6 or more than 6 pre-ovulatory follicles and with peak serum estradiol more

than 1,000 pg/mL. The following options are available to such women:

- Cancel the cycle and reinitiate with a lower gonadotropin dose in the next cycle
- Limited oocyte aspiration
- Conversion to IVF
- Proceed with the cycle and multifetal pregnancy reduction.

Risk of Ovarian Cancer

Earlier studies have suggested a threefold increase in incidence of ovarian cancer in women who undergo ovulation induction.[15] However, the recent reports have not replicated these findings.[16,17] Some reports; however, suggest an increased incidence of borderline tumors.[18] It should be kept in mind, the cancers are over diagnosed in infertile women because of close medical surveillance.

It has; however, been recommended that these drugs should not be used consecutively for more than 6 cycles and not more than a total of 12 cycles. Smallest dose for shortest possible duration should be used.

COMPLICATIONS DUE TO INSEMINATION PROCEDURE

These are rare and not life-threatening. These are:

- Infection
- Trauma and bleeding
- Pain
- Noninfective salpingitis
- Allergic reaction
- Antisperm antibody
- Vasomotor symptoms.

Infection

The risk of infection with IUI is rare and is estimated to be 1.8 per 1,000 women.[19] The reasons for such low risk are:

- The population has already been screened for infection
- The risk of acquiring sexually transmitted disease (STD) during treatment is rare
- Sperm preparation techniques are thought to remove microbes.[20]

Infection can; however, occur sometimes. The sources of infections are:

- Local source: Resident urethral flora, hands, glans penis
- Airborne bacteria in the semen collection room
- Contamination due to faulty technique:
  - Collection in unsterile container
  - Nonsterile preparation techniques
  - Cannula tip touching the vagina
  - Contamination with cervical flora.

The organisms commonly isolated are *Escherichia coli, Neisseria gonorrhoeae, Trichomonas vaginalis*, Streptococcus, Ureaplasma, etc.

Prevention

- Aseptic techniques and quality control should be maintained.
- Sperm wash media can be supplemented with antibiotics.
- Educate patient on proper semen collection techniques.

Administration of prophylactic antibiotics does not alter the infection rates. The role of prophylactic antibiotics is still a matter of debate.

Trauma and Bleeding

IUI is a relatively simple and easy procedure and proper technique can avoid trauma. Trauma and bleeding; however, can sometimes occur due to injury to the internal os or the endometrium by the insemination cannula or by injury to the cervical lip by Allis/Vulsellum.

Bleeding after IUI is associated with low pregnancy rates.[21]

Pain

Pain can occur because of uterine cramps. Severe cramps have been reported in 6-17% of cases.[22] Pain can be due to instrumentation. Also in cases of difficult IUI, trauma to the endometrium can cause release of prostaglandins, which can cause cramping pain. Prostaglandins can also be introduced with seminal plasma. Good semen washing techniques and reducing the volume of inseminate can minimize this problem.

Noninfective Salpingitis

Any foreign substance like sperm preparation ingredients like percoll can irritate the endometrium and can cause noninfective salpingitis. Proper washing of sperms with density gradients can prevent these.

Allergic Reaction

These are rare. Mild reactions may not be seen immediately but can occur later. Severe anaphylaxis can

rarely occur. It can be due to semen itself, ingredients of sperm wash media or due to allergy to penicillin or bovine albumin.

Vasomotor Symptoms

Vasomotor symptoms such as nausea, bradycardia and diaphoresis can occur rarely.

Antisperm Antibody

During IUI, a large dose of antigenic sperms is deposited into the uterine cavity directly, bypassing the cervix, which otherwise acts as a barrier and modifies the antigenic load. The sperms are then cleared by the macrophages into the peritoneal cavity. A high immunogenic load may increase the production of antibodies. Different women; however, have different immune response and most reports do not support the hypothesis of formation of antibodies with IUI.

OTHER COMPLICATIONS

- Abortion
- Ectopic pregnancy
- Accidental insemination with wrong sample.

Abortion

Abortion rate with IUI is estimated to be 20-30%.[23,24] This could be attributed to higher age of these women and increased incidence of multiple pregnancy. Early diagnosis and close monitoring of these patients compared to general population also results in higher reported abortion rates.

Ectopic Pregnancy

The incidence of ectopic pregnancy is higher in women undergoing IUI and other assisted reproductive technology (ART) procedures. The incidence is higher in women with history of tubal disease. Even in those without such history, the incidence is about 5 times higher than in general population.

Accidental Wrong Samples

When more than one sample is processed at one time, there is a possibility of mixing of samples. To avoid such a situation:

- Label all samples
- Use separate syringes and pipettes for separate samples
- Properly identify the sample before loading the cannula
- More than one person should check the sample
- Gynecologist should recheck the identity before inseminating.

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