22 MANAGEMENT OF AZOOSPERMIA

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The diagnosis of azoospermia is established when no spermatozoa can be detected on high-powered microscopic examination of a pellet after centrifugation of the seminal fluid on at least two separate occasions. The World Health Organization recommends that seminal fluid be centrifuged for 15 minutes at 3000 × g or greater [1]

The prevalence of azoospermia is approximately 1% among all men [2] and ranges between 10% and 15% among infertile men [3]. The management of azoospermia basically depends on the underlying cause.

The causes of azoospermia can be divided into three main categories: pretesticular, testicular, and posttesticular.

1. Pretesticular causes of azoospermia include endocrine abnormalities having adverse effects on spermatogenesis (secondary testicular failure) .These are correctable disorders.
2. Testicular causes of azoospermia (primary testicular failure) consist of disorders of spermatogenesis intrinsic to the testes. These are non correctable disorders except for varicocele
3. Posttesticular causes of azoospermia include the obstructive causes and are related to ejaculatory dysfunction or ductal obstructions that prevent sperm from reaching the urethral meatus. These are also correctable.

These causes can also broadly be divided into obstructive and non obstructive azoospermia. Approximately 40% of cases result from obstruction in the ductal system [2].

In azoospermic men, the minimum initial evaluation should include a complete medical history & physical examination. The initial endocrine evaluation should include measurements of total serum testosterone and follicle-stimulating hormone (FSH). Any coexisting infertility factors in the female partner must also be taken into account.

MANAGEMENT

Non Obstructive Azoospermia:

The diagnosis of non obstructive azoospermia (NOA) includes idiopathic as well as identifiable etiologies [4]. Irrespective of the cause the management of patients with NOA usually relies on restoring fertility by the recovery of spermatozoa with a testicular biopsy/sperm extraction procedure and doing in vitro fertilization with intracytoplasmic sperm injection (IVF/ ICSI) [5]. The recovery of sperm cells is successful in only about 50% of cases [1, 3, 6, 7], and the subsequent pregnancy rate after IVF/ICSI is even lower [8].

Noninvasive Approach

These are the tests that can predict sperm retrieval success with testicular biopsy. The noninvasive approach can be used to select NOA patients for possible testicular biopsy and can potentially avoid unwanted interventions.

Serum FSH concentration reflects testicular volume and germ cell content of the testis. Men with an FSH level of 7.6 mIU/mL or a testicular long axis of 4.6 cm may be counselled accordingly [9].That is these men are best treated with therapeutic testicular biopsy and sperm extraction, with processing and cryopreservation for usage in IVF/ICSI if they accept advanced reproductive treatment [9].

Serum inhibin B levels also have been proposed as a marker of spermatogenesis [10]. But the studies are inadequate to determine whether or not a patient should undergo a TESE solely on the basis of a serum inhibin B concentration [11].

Doppler ultrasound imaging has been proposed to identify regions of the testis in which spermatozoa are most likely to be retrieved by TESE [12,13]

AZF microdeletions: Among the different AZF microdeletions of the Y chromosome, the isolated AZFc deletion seems to be associated with a good probability of sperm detection after testicular biopsy or TESE the importance of a karyotypic abnormality is reduced based on the recent finding of a high sperm retrieval rate with TESE in patients with Klinefelter syndrome [14].

Invasive Approach:

Testicular Biopsy: Testicular biopsy techniques can be grouped into broad categories: percutaneous and open (surgical).

1. Percutaneous biopsy techniques can be performed in the office setting. The principal percutaneous testicular biopsy techniques used for sperm recovery in NOA patients include:
   - Fine needle aspiration biopsy (FNAB): FNAB is the simplest biopsy technique used to retrieve spermatozoa. It is performed with needle size varying from 23 to 19 gauge.
   - Large Needle Biopsy (LNB): LNB typically uses relatively larger needles, from 14 to 20 gauge, and provides tissue cylinders or fragments for conventional histologic evaluation as well as sperm retrieval.
2. Open surgical techniques: Open surgical techniques are the most commonly described techniques for sperm retrieval from NOA patients in many comparison studies with FNAB or LNB they obtained higher success rates [4].

   Two different open surgical techniques are most commonly used, the conventional TESE (cTESE) and the new selective mTESE techniques.
   - Conventional TESE: The cTESE technique is performed under general or locoregional anesthesia with an incision made in the scrotal skin; it yields one single large fragment of tissue or multiple smaller fragments from different areas of the testis. This does not require the use of operating microscope. Sperm retrieval occurred more frequently with multiple bilateral biopsies (49%) than with a single bilateral biopsy (37.5%) [15].
   - Microdissection testicular sperm extraction: The mTESE technique involves a near circumferential opening of the tunica albuginea. This requires the use of the operating microscope, to indicate sites of active spermatogenesis [16, 17, 18]. High sperm retrieval rates (35%–77%) have been reported with this technique in NOA [17]. This technique was associated with a reduced risk of testicular tissue damage. The mTESE technique is more successful in sperm retrieval than the standard surgical biopsy when sampling either a single large specimen [19] or multiple specimens [20]. The mTESE technique seems to increase the probability of sperm retrieval even if it prolongs operative time.

Treatment Options For Obstructive Azoospermia

Men with obstructive azoospermia have 2 options:

1) Surgical correction of the obstruction, which may allow the couple to try to conceive naturally, or
2) Retrieval of sperm directly from the epididymis or testis, followed by in vitro fertilization (IVF) or intracytoplasmic sperm injection(ICSI)

Surgical Treatment:

The surgical management of obstructive azoospermia varies with the site of obstruction.

- Obstructions in the vas deferens and epididymis are treated by microsurgical reconstruction.
- Ejaculatory duct obstruction is treated by transurethral resection of the ejaculatory ducts (TURED).

Microsurgical Reconstruction of the Vas Deferens and Epididymis:

Microsurgical vasectomy reversal has high success rate. Sperm returns to the ejaculate after surgery in 70% to 95% of patients, and 30% to 75% of couples expect to achieve pregnancy without assisted reproductive technologies (ART) [21].To avoid the need for additional surgery, should attempts at reconstruction fail, sperm may be retrieved during surgery and cryopreserved for later IVF/ICSI.

Transurethral Resection of the Ejaculatory Ducts (TURED):

Ejaculatory duct obstruction is uncommon but can be treated successfully by TURED where the duct enters the distal prostatic urethra. After TURED, sperm return to the ejaculate in approximately 50% to 75% of men; approximately 20% of couples achieve pregnancy. Complications of TURED occur in approximately 20% of men, including hematuria, hematospermia, urinary tract infection, epididymitis, and a watery ejaculate due to reflux of urine [22].

Sperm Retrieval Techniques: Common methods of sperm retrieval are

1. Open testicular biopsy
2. Microsurgical epididymal sperm Aspiration (MESA)
3. Percutaneous epididymal sperm Aspiration (PESA)
4. Testicular sperm extraction (TESE)
5. Percutaneous testicular sperm Aspiration (TESA)

Other methods that are used less frequently include vassal sperm aspiration and seminal vesicle sperm aspiration guided by transrectal Ultrasonography.

All methods generally provide sufficient numbers of viable sperm for ICSI and often also for cryopreservation. As long as viable sperm can be retrieved, neither the duration of obstruction nor the motility of the sperm affects the outcomes achieved with IVF/ICSI [22,23].The technique of sperm retrieval and the source of sperm (testis, epididymis, vas or seminal vesicle) have no significant effect on pregnancy rates achieved with IVF/ICSI . When surgically retrieved epididymal or testicular sperm are used for ICSI, fertilization rates range between 45% and 75% per injected oocyte ; clinical pregnancy rates range from 26% to 57% and delivery rates range from 18% to as high as 54% [24,25].

Microsurgical vasovasostomy and vasoepididymostomy may be more cost effective than sperm retrievaland IVF/ICSI, particularly for couples who hope to conceive more than a single pregnancy, because a successful reconstruction allows the couple to try and conceive naturally with further intervention. The average time to pregnancy after a successful microsurgical vasectomy reversal is 12 months [21].

Summary:

1. Identify patients at risk for NOA, based on clinical history and prior medical evaluation.
2. Perform noninvasive tests only on select patients who will benefit from invasive testing. Can directly go to invasive testing if clinical scenario alone provides sufficient justification for invasive testing.
3. Decide which invasive test is most appropriate, based on risk-benefit, cost-effectiveness, and local experience with available procedures.
4. Based on the results of the invasive test, provide therapeutic options for the patient.
5. When obstructive azoospermia results from a vasectomy performed less than 15 years before and there are no coexisting female infertility factors, microsurgical reconstruction of the reproductive tract generally is preferred over sperm retrieval and IVF/ICSI.
6. When azoospermia results from epididymal obstruction the choice between microsurgical reconstruction and sperm retrieval/ICSI should be individualized.
7. Sperm retrieval and IVF/ICSI generally is the best choice of treatment for obstructive azoospermia when
   a) The female partner is over age 37,
   b) There are coexisting female infertility factors that require IVF, and
   c) The likelihood for success with sperm retrieval/ICSI is greater than with surgical treatment.

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23 OVARIAN HYPERSTIMULATION SYNDROME (OHSS)

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OHSS is an exaggerated response to ovulation induction therapy. It is typically associated with exogeneous gonadotropin stimulation. It is a syndrome comprising with marked ovarian enlargement, high serum estradiol and extra vascular exudate accumulation, secondary to increased vascular permeability and significant shift of proteins and fluid, from vascular tree primarily into the peritoneal cavity. Depletion of intra vascular volume results in haemoconcentration, diminished organ perfusion and propensity for thromboembolism.

Incidence

- Mild 20 – 33 % of IVF cycle
- Moderate 3 - 8%
- Severe 0.1 – 0.5%

Etiopathogenesis

Stimulated ovaries

↓

Release vasoactive mediator

(Prostaglandins, cystokines, VEGF, renin, angiotensin, endothelin)

↓

Endothelial injury and vasodilation

↓

3rd space fluid loss with circulatory dysfunction

↓

Haemoconcentration and end organ failure.

OHSS Classification

Early Onset	Late Onset
Related to ovarian response and exogenous hCG (3-9 days after hCG)	Endogenous hCG produced by implanting embryo (more than 10 days)

Ovarian Hyperstimulation Syndrome (OHSS) *contd.*

(Golan etal)

Mild Hyper stimulation	Moderate	Severe
Grade 1 – Abdominal distension and discomfort	Grade 3 – Grade 2 + USG evidence of ascites.	Grade 4 - grade 3 + clinical e/o ascites and or hydrothorax and breathing difficulties
Grade 2 – Grade 1 + nausea, vomiting and diarrhoea, bloodenlarged ovaries 5-12cm		Grade 5 – Grade 4 + haemo concentration, increased viscosity, coagulation abnormality and diminished renal perfusion.

Daniel Navot et al, 1992

Severe OHSS	Critical OHSS
• Clinical ascites, hydrothorax • Haemo concentration – PVC > 45%, TC15000/ ml • Oliguria with normal serum creatinine • Liver dysfunction • Anascarca, ovarian size>12cm	• Tense ascites • Worsening haemo concentration PCV >55% TC>25000/ml • Oliguria with elevated serum creatinine>1.6cr • Creatinine clearance<50ml/min, renal failure • Thromboembolic phenomena, ovarian size>12cm

Risk Factors

The following factors increase the risk independently for developing OHSS

- Young age
- Low body weight
- Polycystic ovarian syndrome
- Higher doses of exogenous gonadotropins
- High absolute or rapidly rising serum E2 levels
- Previous episodes of OHSS

Signs and symptoms are

- Distension of lower abdomen
- Nausea and vomiting
- Dyspnoea and respiratory distress

- Diarrhoea
- Rapid weight gain
- Ovaries enlarged up to >12cm
- Hypotension
- Pleural effusion [more frequently on the right side)
- ARDS
- Pericardial effusion
- Ascites
- Oliguria and anuria
- Multiple organ failure – death (01/500,000 cycle)

Management

Primary Prevention:

- Reducing the starting dose of gonadotropin for ovulation induction.
- Use of chronic low dose step up protocols in PCOS
- Limited ovarian stimulation, which involves stimulation of follicle only to a size of 12mm.
- Antagonist based protocols (Cochrane review 2009) are short and simple with good clinical outcome and significant reduction in incidence of severe OHSS.
- Re initiation of antagonist 3 days after oocyte retrieval, in cases diagnosed with severe OHSS for 1 week (Laina Setal, RBM on line 2007)
- Avoiding hCG for luteal phase support
- In Vitro Maturation – in patient with PCOS, patients at risk of OHSS

  (Not widely used owing to reduced live birth rate compared to conventional IVF).

Secondary Prevention:

- Coasting - withholding further gonadotropin stimulation and delaying hCG administration until E2 levels plateau or decrease significantly.

  Coasting does not completely avoid severe OHSS but significantly reduces the incidence and severity. Some oocytes may be lost specially if coasting is more than 4 days; it also affects endometrial maturation status and reduces the chances of pregnancy.
- Reduced dose of hCG - compared with the standard dose of 10,000 i.u., doses of 5,000 i.u. have been used successfully without impairing clinical outcome.
- Use of alternative agents for triggering ovulation like GnRH agonist or Recombinant LH but are associated with reduced pregnancy rates and have poor cost benefit ratio.
- Cryopreservation of all the embryos - early OHSS may occur but reduces severity and duration.

- Intravenous Albumin – it is a volume expander and has direct action on membrane permeability.

  It is a plasma binding protein that may bind to the vaso active agents responsible for the development of OHSS and facilitate there removal from the circulation.

- Hydroxyethyl starch solution (6%) can be infused at the time of oocyte collection and repeated after 48hrs later. It is cheaper, potentially safer alternative to albumin.

- Dopamine agonist it acts on the dopamine receptor 2, inhibits VEGFR – 2 dependent vascular permeability and angiogenesis. It is recommended in a dose of 0.5mg/ day for 8 days from the day of hCG. It has time and dose dependent effect.

Out Patient Management

Patient with mild manifestations of OHSS can be managed on an outpatient basis. Treatment usually requires only oral analgesics and counseling regarding the signs and symptoms of progressing illness. Intercourse is best avoided as it may be painful and may increase the risk of ovarian rupture.

Treatment of worsening OHSS typically requires antiemetic and more potent analgesic. Most patients still can be effectively managed and monitored on an outpatient basis, but they require more careful evaluation including frequent physical and ultrasound examination (to detect increasing ascites), daily weight measurement, and serial laboratory determination of hematocrit, electrolytes, and serum creatinine. Careful monitoring is essential and should include at least daily communication, if not examination, to ensure that progression to more severe disease is promptly recognized.

Recommendation for the outpatient management of persistent and worsening OHSS includes:

1. Oral fluid intake should be maintained at no less than 1 L per day, any of the commercially available electrolyte supplemented drinks is preferable to other beverages.
2. Strenuous physical activity should be avoided as risk of ovarian torsion increases when the ovaries are significantly enlarged. Light physical activity should be maintained to the extent possible. Strict bed rest is unwarranted and may increase risk of thromboembolism.
3. Weight should be recorded daily, as well as the frequency and/ or volume of urine output. Weight gain of > 2 pounds repeated physical examination, ultrasound, and laboratory evaluation to include hematocrit, electrolytes, and serum creatinine.
4. Pregnant patient with OHSS must be monitored very closely because risk of progressing to severe disease is particularly high, as continuous stimulation by rapidly rising endogenous concentrations of serum hCG.
5. In ART cycles, it may be necessary to consider cryopreserving all embryos and deferring transfer to subsequent cycle after symptoms have completely resolved. Although pregnancy rates in frozen embryo transfer cycles are generally lower than in fresh cycles, this approach may reduce the risk for developing severe OHSS without a marked decrease in pregnancy rates per cycle.

Hospitalization

Serious illness requiring hospitalization is relatively uncommon but by no means rare. Hospitalization may be required based on severity of symptoms, analgesic requirements, and other social considerations (availability of responsible adult supervision, and assistance with child care).

Given the scope and severity of symptoms and the potential for complications, most women with OHSS who are seriously ill merit hospitalization for more careful monitoring and aggressive treatment. No one symptom or

sign is an absolute indication, but hospitalization should be considered when one or more of the following are present:

- Severe abdominal pain or peritoneal signs
- Intractable nausea and vomiting that prevents ingestion of food and adequate fluids
- Severe oliguria or anuria
- Tense ascites
- Dyspnoea or tachypnea
- Hypotension (relative to baseline), dizziness, or syncope
- Severe electrolyte imbalance (hyponatremia, hyperkalemia)
- Hemoconcentration
- Abnormal liver function tests

Laboratory findings in women with serious illness resulting from OHSS include .

- Hemoconcentration (hematocrit> 45%)
- Leukocytosis (white blood cell count > 15,000)
- Electrolyte imbalances (hyponatremia: sodium <135mEq/l; hyperkalemia: potassium>5.0mEq/l)
- Elevated liver enzymes
- Decreased creatinine clearance (serum creatinine >1.2; creatinine clearance <50mL/min)

Recommendations for the evaluation and monitoring of hospitalized patients with OHSS include the following:

- Vital signs (every 2-8 hours, according to clinical status)
- Weight (recorded daily)
- Complete physical examination (daily, avoid bimanual examination of the ovaries due to risk of ovarian rupture)
- Abdominal circumferences (at the naval, recorded daily)
- Monitoring fluid intake and output (daily or more often)
- Ultrasound examination (ascites, ovarian size), repeated as necessary to guide management or Paracentesis
- Chest X-ray and echocardiogram (when pleural or pericardial effusion is suspected), repeated as necessary
- Pulse oximetery (for patients with symptoms of pulmonary compromise)
- Complete blood count (daily, or more often as needed to guide fluid management)
- Electrolytes (daily)
- Serum creatinine or creatinine clearance, urine specific gravity, repeated as necessary

Ovarian Hyperstimulation Syndrome (OHSS) *contd.*

Careful and frequent re-evaluation of the hospitalized patient with severe OHSS is essential. Complaints of increasing abdominal pain and distension demand immediate attention, remaining mindful that pain and ascites can mask ovarian rupture and acute intra-abdominal hemorrhage. Serial clinical and laboratory evaluation provide the means to monitor progression of illness, to judge the response to treatment, and to recognize evidence of resolution.

Fluid management

Correction of hypovolemia, hypotension, and oliguria has utmost priority

- Strict intake and output monitoring
- IV infusion in volumes is necessary to maintain urine output of at least 30ml/hr and reverse the haemoconcentration
- 5 % dextrose is preferable to lactated Ringer's solution.
- Albumin (25%) in doses of 50gm in 200ml at 50ml/hr infused over 4 hrs and repeated at 4-12 hr intervals as necessary is an effective plasma expander when infusion of normal saline fails to achieve or maintain haemo dynamic stability and adequate urine output
- Treatment with diuretics (furosemide 20mg iv) may be considered after an adequate intravascular volume has been restored (haematocrit <38%).

Paracentesis

Ultra sound guided Paracentesis may be indicated for patients with

- Ascites (that causes pain) ,
- Compromised pulmonary function
- Oliguria/ anuria (that does not improve with fluid management.)

A transvaginal/ transabdominal ultrasound guided approach may be used to avoid inadvertent puncture of vascular ovaries with distended large luteal cysts. The optimal volume of fluid that should be removed on any one occasion, and over what interval of time, is not well established. Intra venous colloid replacement should be considered for women who have large volume of ascitic fluid drained.

Paracentesis will generally be effective in resolving hydrothorax and thoracocentesis may be reserved for those with bilateral or severe effusion that persist.

Thomboprophylaxis

Thromboembolisim is a life threatening complication of severe OHSS and prophylaxis warranted. Thomboprophylaxis should be provided for all women admitted in the hospital with OHSS and continued until discharge from hospital and possibly longer depending upon other risk factors (RCOG 2006).

Full length venous support stockings and heparin (5000 units S.C. daily) should be considered.

The reported incidence of thrombosis with OHSS ranges between 0.7 and 10%.

Ovarian Hyperstimulation Syndrome (OHSS)

Summary

- Experience with ovulation induction therapy and knowledge of OHSS pathophysiology, risk factors, and clinical features are key to preventing and managing OHSS.
- Mild manifestations of OHSS are fairly common, occuring in up to third of exogenous gonadotropin-induced super ovulation cycles.
- Worsening symptoms of OHSS can still usually be managed on an outpatient basis, but frequent monitoring and evaluation are essential.
- Serious illness resulting from OHSS is much less common, but it can be life threatening.
- Hospitalization may be necessary for patients with serious illness resulting from OHSS.

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ART IN POOR RESPONDERS

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Introduction

Although the first successful in-vitro fertilization (IVF) reported in 1978 resulted from a natural unstimulated cycle, it became subsequently clear that ovarian stimulation resulted in a higher number of oocytes retrieved and higher pregnancy rates (PR). Today, controlled ovarian stimulation prior to IVF or ICSI is a practice accepted worldwide. However, in 5-24% cases, the female partner's response to ovarian stimulation is less than optimal, resulting in the retrieval of a fewer number of oocytes. These patients are termed poor responders. Poor responders have a higher incidence of cycle cancellation and lower fertilization, pregnancy and implantation rates. [1] The purpose of this chapter is to help ART specialists identify these poor responders and make them aware of certain modified IVF stimulation protocols which will optimize the management of such patients, increasing their oocyte recovery and pregnancy rates. These protocols can also be used with similar benefit in poor responders undergoing intrauterine insemination (IUI) cycles.

Definition Of Poor Responders

There is no universal definition of poor responders. Apart from those patients who show a poor response by virtue of their age, high basal FSH or low AMH levels, there is another subset of patients who have normal FSH or AMH levels but are diagnosed retrospectively as poor responders, after they show a poor response (in terms of oocyte recovery) to adequate ovarian stimulation. We find the following definition most acceptable as per our clinical experience: "Three or fewer oocytes retrieved and/or serum E_2 levels < 500 pg/ml at the time of hCG administration in an IVF cycle"

Etiology

Advanced age >37.5 years: At birth, there are approximately 1-2 million oogonia which decline to 3-5 lakhs by puberty. Of these, about 400-500 ovulate in the reproductive period. When the number of resting follicles falls below 1000, menopause sets in. In a normal healthy woman accelerated loss & qualitative decline of follicles, start at 37.5 years, when only 25000 resting follicles remain. Fertility declines rapidly after 37.5 years and becomes almost zero at age 41.

Premature ovarian insufficiency (POI): In some women, there is early accelerated decline of follicles in number & quality, much before the stipulated 37.5 years. This is early ovarian aging leading to POI and eventually premature ovarian failure (POF). The factors responsible are genetic, immunological, chronic infections like hepatitis B & HIV, previous ovarian surgery, pelvic inflammatory disease and chronic smoking.

Predicting Ovarian Reserve [2]

For prediction of ovarian reserve, the ideal test is the response of the ovaries to ovarian stimulation with gonadotropin injections.

Advanced age > 37.5 years

Hormonal profile

- High levels of serum FSH (>12 mIU/ml) on cycle day 2/3
- Elevated levels of serum E_2 (>75 pg/ml) on cycle day 2/3
- Decreased levels of serum Inhibin B (<45 pg/ml) on cycle day 2/3
- AMH in unstimulated cycle: < 1.05 ng/ml or < 7 pmol/litre [2]

Trans-vaginal ultrasound on day 2/3 of menses

- Antral follicle count < 6 in both ovaries
- Ovarian volume < 3cc

Unexplained poor responders: Patients whose response to adequate ovarian stimulation is poor despite their predictive tests not being suggestive of low ovarian reserve.

STRATEGIES TO IMPROVE THE OVARIAN RESPONSE

MODIFICATIONS OF CONVENTIONAL PROTOCOLS

Higher dosage and duration of gonadotropins

The simplest approach to increase the magnitude of the ovarian response is to increase the dose and duration of exogenous gonadotropins during subsequent stimulation. The starting dose of gonadotropins for poor responders should be 300 IU/day and can be increased upto 450 IU/day. [2] Daily doses above 450 IU rarely produce a meaningful improvement in PR. [3]

GnRH agonist (GnRHa) long protocol

- Reducing the dose of GnRHa

  After adequate pituitary suppression is achieved with a conventional dose of GnRHa, the dose is reduced to 1/4th to 1/5th, from day 2 of menses when gonadotropin stimulation is started. This results in shorter duration and dose of stimulation, better estradiol levels with more oocytes and embryos for transfer.

- Stop agonist regimen

  In this regime, after pituitary suppression is achieved instead of reducing the dose, the GnRHa is stopped. This reduces ovarian suppression and increases the ovarian response. Despite the early discontinuation of the agonist, the incidence of premature LH surge is low. But no improvement in PR was found. [2]

Flare-up GnRH agonist short and ultra-short protocols

These involve early follicular phase commencement of the GnRHa, with minimal delay before the onset of gonadotropin administration. There are two theoretical advantages: first, the ovarian suppression is not excessive; and second, the initial stimulation of the GnRH receptors & secretion of endogenous gonadotropins enhances the effects of the exogenously administered gonadotropins. [2]

GnRH antagonist regimens

These aim to avoid the premature LH surge & help to utilize the maximum ovarian oocyte cohort by avoiding the GnRH agonist induced suppression of the ovarian receptors at the follicular recruitment stage. [2] Therefore they are associated with shorter duration & dose of stimulation, reduced patient costs and shorter downtimes

between consecutive cycles. However, it does not add to the existing ovarian response and its superiority in terms of PR is yet to be established. [4]

Regimes Improving The Cohort Of Follicles Recruited

Pre-treatment

Oral contraceptive (OC) pills

Pretreatment with OC pills (in the previous cycle) reported higher estrogen levels, improved synchronization of the follicular cohort, more mature follicles, lower cancellation rates, and higher number of oocytes and PR. [2,5]

Luteal estradiol

The number of oocytes retrieved is determined by the size of the follicle pool that enters the follicular phase. Follicle growth is a 3-month process which is gonadotropin independent. [6] Estradiol valerate is given in the dose of 2.5 mg/day from day 25 of previous cycle till menses. Luteal estradiol attempts to synchronize and increase the initial follicle pool, leading to more oocytes but not necessarily more pregnancies. [6,7]

Dehydroepiandrosterone (DHEA)

Current evidence suggests that DHEA improves ovarian function, increases PR and by reducing aneuploidy, lowers miscarriage rates. Androgens promote preantral & antral follicle growth and reduce follicular atresia. DHEA increases IGF-1 levels and hence over time also objectively improves ovarian reserve. DHEA thus, represents the first agent beneficially affecting the aging ovarian environment. The dose of DHEA is 25 mg thrice a day for maximum of 15 weeks. Improvement in AMH levels can be used to evaluate the drug response. [2]

Adjunctive Therapies

Testosterone patches

Granulosa cell stimulation by FSH is an androgen-modulated process. Androgens are also positive regulators of follicular development, augmenting follicular FSH-receptor expression in granulosa cells. Testosterone therapy is commenced the day when pituitary–ovarian suppression is complete. Daily single transdermal testosterone patch (2.5 mg/day) is applied on the thigh at night and removed always at 09.00 hours in the morning. This transdermal delivery system maintains stable testosterone levels. The dose used is 20 µg/kg/day for 5 days. Thus, in each patient, the patch is applied at night at a time aimed to leave it in place for a predetermined number of hours to provide the desired daily dose. Gonadotropin ovarian stimulation is started the day following last testosterone patch application. [8]

Letrozole and gonadotropins

Aromatase inhibitors block the conversion of androgen to estrogen in the follicle and increase local androgen levels. This seems to increase the FSH sensitivity of the follicle. In addition, by inhibiting feedback mechanisms, FSH output from the pituitary gland is increased, and this will maximize the response to the stimulatory efforts. The dose is 2.5mg/day from day 2 to 6 of the cycle and gonadotropins were started from day 4. [9]

Growth hormone (GH) or GH-releasing factor

In a meta-analysis of randomized trials, GH was reported to increase the PR by approximately three to fourfold respectively, compared with placebo. It was not effective in increasing ovarian response but improved embryo quality and intrafollicular E2 levels. [5] Usually, 4 to 12 IU GH is administered subcutaneously from the day of ovarian stimulation with gonadotropins. Similar effect can be achieved by GH-RF administration because it increases the endogenous levels of GH. [2]

Dopamine Agonists: Bromocriptine-rebound (BR) protocol [10]

Bromocriptine is given daily (2.5 mg/day) from day 5 of the preceding cycle until 7 days before gonadotropin stimulation. The numbers of follicles, fertilized oocytes, and embryos with superior morphology were higher. Rates of clinical pregnancy and live birth delivery per cycle were also significantly higher.

Other agents not supported by evidence but tried with some benefit in individual studies are pyridostigmine, glucocorticosteroids, nitric oxide donors such as L-arginine and low dose aspirin.

Role of cytoplasmic or mitochondrial transfer

Ovarian insufficiency is associated with low mitochondrial DNA content, reflecting cytoplasmic immaturity, characterized by poor oocyte & embryo quality. The low mitochondrial mass is insufficient to provide the necessary energetic reserves during follicular growth. The use of anti-oxidants for this purpose is being explored. Also, further research should allow us to establish whether cytoplasmic or mitochondrial injections into the oocyte will help improve its quality and thus the PR. [11]

Conclusion

Optimizing the treatment protocols for poor responders to give them a pregnancy of their own genetic lineage is a moral and ethical issue. We feel that it is the duty of every ART specialist to address this issue with respect, dedication & care, so as to achieve the requisite goal. It is important for us to understand that, all these poor responders, should be given an option to try IVF/IUI with these modifications, for at least for 1-2 cycles before surrendering to donor oocytes.

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