



**Dr. Rupin Shah**  
Consultant Andrologist & Microsurgeon,  
Lilavati Hospital & Research Centre, Mumbai



**Dr. Ajay S. Shetty**  
Consultant Urologist,  
Bangalore Baptist Hospital, Bangalore

### Introduction

Approximately 10-15% of all couples seek fertility assessment<sup>1</sup>. With a greater participation of women in workforce and the associated delay in the ages of marriage and first child bearing, infertility services are being increasingly utilized. With the advent of assisted reproductive techniques, and the tremendous success it has enjoyed, the evaluation of the male and an attempt at curative treatment is often overlooked. Male factor is involved in about half of the infertility cases<sup>2</sup>. Therefore, identifying the pathology and treating the male may allow couples to improve their fertility potential and conceive through natural intercourse.

Treatment options in Oligoasthenoteratozoospermia (OATS):

1. Medical therapy general or specific
2. Surgical therapy
3. ART Intra Uterine Insemination or Intra Cytoplasmic Sperm Injection

Specific medical management of OATS is based on identifying reversible causes of infertility and treating them with appropriate medications to achieve a pregnancy. Despite the advancements in diagnostic methodology, no identifiable cause can be found in 25% of infertile males<sup>3</sup>. This is referred to as Idiopathic Oligoasthenoteratozoospermia. These patients are treated with nonspecific empirical medications based on theoretical concepts, in an attempt to improve semen parameters and fertility potential.

This article will review the specific and nonspecific medical treatment of OATS. But first, it is essential to know who the candidates are for a trial of medical therapy? And who should be counseled for ART.

Factors that influence choice of therapy in OATS:

1. *Age of the couple and duration of infertility:* A young couple with a short trying time should be given the option of medical therapy in order to buy time to achieve a natural pregnancy. On the other hand, an older couple with a much longer trying time should be counseled to move towards ART.
2. *Severity of OATS* and realistic chances of improvement expected a patient with severe OATS (less than 5 million/ml with very poor progressive motility) with no obvious reversible factors is more likely to benefit from ART.
3. *Past illness causing irreversible damage:* For example, a patient who had post-mumps orchitis and testicular atrophy, or who was operated for undescended testes. In such patients, it is unlikely that medical therapy will help.
4. *Reversible, correctable gonadotoxic factors?* If there is occupational exposure to gonadotoxins (heat, chemical fumes), heavy smoking, recent febrile illness, accessory gland infections, etc., then such patients can be given supportive medical therapy to buy time for improvement of semen parameters once the gonadotoxic factors are eliminated/modified.



5. *Treatment history* is imperative. It's important to know what drugs a patient has already tried in the past (whether they were effective or not) so there is no repetition. If various drugs have already proved ineffective there is no point in giving further medical therapy.
6. *Socioeconomic status* of the couple should also be considered when deciding medication since many empirical drugs are rather expensive.
7. *Psycho-social pressures* on the couple play an important role in decision making. In a couple who is socially hard-pressed for a baby, less time should be spent on medical therapy.

#### Specific Medical Therapy

With history, physical examination and specific investigations, it is possible to diagnose and treat certain specific medical conditions that will contribute to OATS.

1. *Chronic Scrotal Fungal Dermatitis*: This can affect fertility by thickening the scrotal skin and thus increasing the local temperature. This is treated with topical antifungal plus steroid creams.
2. *Genital Tract Infection*: The World health organization (WHO) defines leucocytospermia as seminal white blood cells (WBC) levels more than or equal to  $1 \times 10^6$  /ml (WHO 1999) with the prevalence among male infertility patients being about 10-20%<sup>4</sup>. The clinician must ensure that the laboratory should clearly differentiate between leucocytes and immature germ cells using cytologic staining or immunohistochemical techniques. All men with elevated seminal WBC levels ( $>1 \times 10^6$ /mL) should be evaluated for a genital tract infection or inflammation, and a semen culture should be performed. Common organisms responsible are *Streptococcus fecalis* and *Escherichia coli*, *Chlamydia trachomatis* and *Ureaplasma urealyticum*. Because of the difficulty of culturing chlamydia or ureaplasma we often give Doxycycline 200 mg/day on an empirical basis for 15 days and then start antibiotics as per culture reports. Commonly used are: Fluoroquinolones 0.5 to 1 g/day, Cotrimoxazole (Sulfamethoxazole 800 mg, Trimethoprim 160 mg) or Erythromycin 1.5 to 2 g/day. These drugs are administered for 2 to 3 weeks<sup>5</sup>. However, culture-negative patients with proven leukocytospermia should be treated with anti-inflammatory therapy and frequent ejaculation because empiric antibiotic therapy generally provides no benefit and may be harmful<sup>6</sup>. In cases of refractory leukocytospermia, sperm washing can be performed before intrauterine insemination to remove the white cells.
3. *Immunologic Infertility*: Oral prednisolone is commonly used to suppress antibody production, but no double-blind, randomized trial has confirmed their efficacy. Studies following different protocols report pregnancy rates between 0 to 44%<sup>7,8</sup>. Studies in which treatment was continued for more than 3 months reported a significant increase in the number of pregnancies amongst those receiving prednisolone compared with placebo<sup>9</sup>. ICSI is considered to be the treatment of choice for patients with severe sperm autoimmunity<sup>10</sup>. Recently, higher fertilization rates during in vitro fertilization (IVF) were reported in patients with antisperm antibodies and immunosuppressive therapy compared to IVF alone<sup>11</sup>. Thus, treatment of antisperm antibodies using corticosteroids should not be prescribed routinely, but it can be considered in patients with antisperm antibodies and earlier failed fertilization during IVF or ICSI. High doses of prednisolone should be avoided even on short term due to the rare but catastrophic risk of avascular necrosis of femoral head. We use the following low-dose regimen in men with proven high titres, or OATS with clinical evidence of chronic epididymitis: tablet prednisolone 5 mg, thrice-a-day for 10 days, then twice-a-day for 10 days, then once-a-day for 10 days.
4. *Chronic Epididymo-Orchitis*: Many subfertile men have clinical evidence of chronic filarial epididymo-orchitis residence in an endemic area, enlarged adherent epididymis, thickened cord, lax hydrocoele, h/o hydrocoele surgery, h/o testicular swelling with fever, and occasionally ultrasound evidence of the "filarial

dance". Such men sometimes show good improvement in semen parameters after a course of anti-filariatherapy (DEC 100mg thrice-a-day for 20 days in combination with doxycycline 100mg twice-a-day for 10 days) followed by low dose steroids as given above.

Specific surgical therapy:

Varicocele ligation can play a useful role in selected cases but a discussion on this controversial topic is outside the scope of this article.

Nonspecific or empirical therapy:

In patients with idiopathic OATS, a variety of empirical medical therapies have been recommended. Although there are numerous reports that support a multitude of compounds, the vast majority are nonrandomized studies and unfortunately no medical therapy has demonstrated consistent efficacy in multiple, rigorous, well-controlled, randomized, placebo controlled trials<sup>12</sup>. Because of isolated case reports and small series demonstrating efficacy of some agents, there is continued hope that they may be effective in select subpopulations of men with idiopathic reproductive dysfunction.

In this article, we address the commonly used non-specific medications, their rationale and also assess the evidence for their utility in the management of idiopathic male infertility. Our aim is to aid physicians to choose the most suitable treatment from several therapeutic options, and be able to counsel the couples appropriately.

Non-specific treatments include

- A. Hormonal agents: Androgens, Antiestrogens, Aromatase inhibitors, Gonadotropins.
- B. Antioxidants : Glutathione, Lycopene, Vitamin -E
- C. Sperm vitalisers : L-carnitine, Co-enzyme Q 10
- D. Nutritional supplements : Folic acid, Zinc, Multivitamins, Trace elements
- E. Miscellaneous: Indomethacin, Kallikrien, Low dose corticosteroids.
- F. Elimination of gonadotoxic factors

Hormonal Agents :

- Androgens :
  - Rationale
    - Direct therapy: Exogenous androgens, administered at a dose that will not influence the pituitary-gonadal axis, may have a direct stimulatory effect on spermatogenesis or influence sperm transport and maturation through an effect on the Epididymis, Vas deferens and Seminal vesicles.
    - Rebound therapy: High doses of exogenous androgens will suppress the H-P-T axis and result in azoospermia. Subsequently, after cessation of androgens, the gonadotropin levels will rise again, during which period there may be a rebound increase in sperm counts above baseline.
- Drugs used and dosage
  - Direct therapy : Mesterolone 25mg thrice daily;  
  : Testosterone undecanoate 40mg two to four capsules daily.
  - Rebound therapy: has been given up because of uncertain results and risk of permanent azoospermia

- Antiestrogens :
  - Rationale: Antiestrogens inhibit the negative feedback effect of estrogen by blocking estrogen receptors in the hypothalamus, which in turn increases endogenous gonadotropin secretion. In turn, FSH and LH stimulate Sertoli and Leydig cells with a possible improvement in spermatogenesis
  - Drugs used and dose :
    - i. Clomiphene citrate : 25mg daily, or on alternate days
    - ii. Tamoxifen citrate : 10 to 20 mg daily
- Aromatase Inhibitors :
  - Rationale: Estrogen has a potent negative feedback effect on gonadotropin secretion. Obese men have excessive aromatization, in their fat cells, of Testosterone to Estrogen resulting in excess estrogen and an altered Testosterone to Estrogen ratios (T/E). Aromatase inhibitors correct this by inhibiting the peripheral conversion of Testosterone and may thereby enhance spermatogenesis.
  - Drugs used and dose :
    - i. Letrozole 2.5mg daily orally
- Gonadotropins :
  - Rationale: Some patients with idiopathic infertility may have a subclinical endocrinopathy which results in abnormalities in the bio-activity, half-life or pulsatility of gonadotropin secretion<sup>13</sup>. Such men may benefit from exogenous gonadotropins despite normal levels on immunoassay.
  - Drugs used: Human chorionic gonadotropin (HCG) (1500 IU i.m 3 times per week), Human menopausal gonadotropin (HMG) (37.5-75 IU i.m 3 times per week) ,

#### Antioxidants:

- Rationale: Elevated seminal Reactive Oxygen Species (ROS) levels have been recognized as an independent marker of male factor infertility, irrespective of whether patients have normal or abnormal semen parameters<sup>14</sup>. Spermatozoa are particularly susceptible to oxidative stress- induced damage. Antioxidants in seminal plasma are the most important form of protection available to spermatozoa against ROS<sup>15</sup>. Many studies have supported the use of exogenous antioxidants in the treatment of idiopathic infertility.
- Drugs used and dose: Glutathione 250mg daily (50-600mg/day), Lycopene 4-8 g daily, Vitamin E 400 to 800 mg daily.

#### Sperm Vitalisers:

- Rationale: Act through varying mechanisms with a common end-point of energizing the sperm and making them more capable of fertilization. They may have a role in sperm maturation during the transit through the epididymis. Some of them have an antioxidant action in addition.
- Drugs used and dose : L-Carnitine and Acetyl Carnitine 1 g, thrice-a-day;  
: Coenzyme Q10 100-300 mg per day.

Nutritional Supplements :

- Rationale: In our country, majority of the people from the lower socioeconomic strata are nutritionally depleted and therefore may not have the necessary levels of vitamins and trace elements to facilitate spermatogenesis.
- Drugs used : multivitamin combinations with zinc, selenium, folic acid, and B12

Miscellaneous :

- Rationale: Some of these therapies have aimed at improving sperm quality by boosting the Kallikrein-Kinin system(Kallikriens) or by interfering with the production of prostaglandins (Phosphodiesterase inhibitors, Nonsteroidal anti-inflammatory agents)
- Drugs used: Kallikriens 600 IU daily; Indomethacin.

Elimination of Gonadotoxic Factors

Elimination of chronic exposure to heat at the workplace (furnace, kitchen, etc) or in leisure activities (sauna, steam bath), cessation of heavy smoking, avoidance of exposure to pesticides (DDT spray) or chemical fumes (aromatic amines), reduction of excessive stress, regularization of diet and lifestyle can also help some men significantly.

Table 1 illustrates the relevant evidence in literature regarding the various medical therapies available.

Treatment option	Studies supporting	Best available evidence	Study outcome	Comments
Carboxotrophic	Uncontrolled studies (15,17)	Systematic review with meta-analysis (18)	Potentially effective, but more evidence needed to confirm the findings.	Probably costly, lowest effectiveness, but may be in subset group of patients.
Anti-oxidants	Uncontrolled studies (19,20)	Double blind placebo controlled RCT Systematic review with meta-analysis (22)	Not enough to confirm evidence	Low cost, minimal side effects, but for the cost of oxidative stress management.
Acemastat inhibitors	Uncontrolled studies (23)	Double blind placebo controlled (24)	No effect on sperm parameters or pregnancy outcomes. Trials necessary	Expensive. Lower effectiveness as mentioned can be associated with a low TFS rates.
Androgens	Uncontrolled study (25), Placebo controlled (26)	Systematic review with meta-analysis (27)	No effect on sperm parameters or pregnancy rates	Significant risk of azoospermia, liver dysfunction, gynaecomastia
L-Carnitine	Uncontrolled multicenter study (28)	RCT (29,30)	Potentially more cost and established by type II level of evidence pregnancy data.	Expensive
Coenzyme Q10	Single study, uncontrolled study (31)		Impression not by no pregnancy data.	Insufficient to guide clinical decisions.
Combination therapy (vitamin + antioxidants)		Double blind RCT (32)	Potentially effective but numbers are small.	More studies needed to confirm findings
Combination therapy (vitamin + antioxidants + androgens)		RCT (33)	Potentially effective	More studies needed to confirm findings

Table 1 : Available evidence in the medical treatment of male infertility

Conclusions:

As physicians taking care of couples with OATS, it is our duty to give the patients a very clear road map of their course of therapy. Therapy must be individualized and it is mandatory that a treatment timeline and endpoints be established prior to initiation of medical therapy. When empiric pharmacologic therapy is going to be used, treatment should last at least 3 months to incorporate a full 74-day spermatogenic cycle, and should be

followed by a semen analysis. If there is significant improvement then the medications should be continued and further improvement monitored monthly. If there is no improvement then the medication should be changed. Patients must be counseled regarding the inconsistent response to medical therapy and to have realistic expectations from the same. Most importantly, we must not be guilty of wasting precious time and money over medical therapy when the circumstances call for assisted reproductive therapy. Figure 1 summarizes a practical approach to the management of OATS.

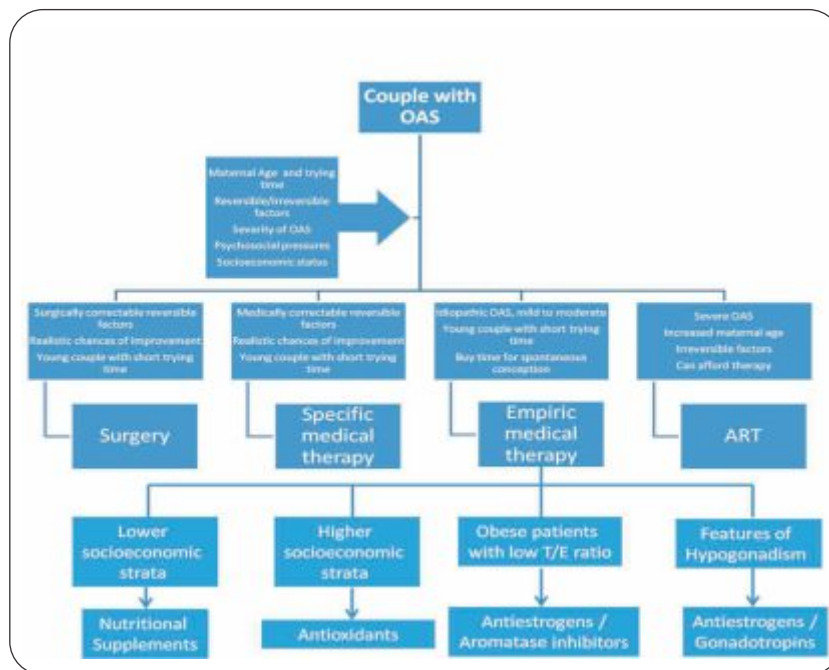


Figure 1 :

## References :

1. Snick, H.K., Snick, T.S., Evers, J.L. and Collins, J.A. (1997) The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. *Hum. Reprod.*, 12, 1582-1588.
2. Comhaire, F.H., de Kretser, D.M., Farley, T.M. and Rowe, P.J. (1987) Towards more objectivity in diagnosis and management of male fertility. *Int. J. Androl.*, (Suppl. 7), 1-53.
3. Greenberg S, Lipshultz L, Wein A. Experience with 425 subfertile male patients. *JUrol* 1978;119:501.
4. Wolff H. 1995. The biologic significance of white blood cells in semen. *Fertil Steril*, 63:114357.
5. Haidl G, Schill WB. 1991. Guidelines for drug treatment of male infertility. *Drugs*, 41:608
6. Yanushpolsky EH, Politch JA, Hill JA, et al. 1995. Antibiotic therapy and leukocytospermia : a prospective, randomized, controlled study. *Fertil Steril*, 63:1427.
7. Shulman JF, Shulman S. 1982. Methylprednisolone treatment of immunologic infertility in male. *Fertil Steril*, 38:5919.
8. Hendry WF, Treehuba K, Hughes L, et al. 1986. Cyclic prednisolone therapy for male infertility associated with autoantibodies to spermatozoa. *Fertil Steril*, 45:24954.
9. Hendry WF, Hughes L, Scammell G, et al. 1990. Comparison of prednisolone and placebo in subfertile men with antibodies to spermatozoa. *Lancet*, 335:858.
10. Check ML, Check JH, Katsoff D, et al. 2000. ICSI as an effective therapy for male factor with antisperm antibodies. *Arch Androl*, 45:12530.
11. Haidl G. 2002. Management strategies for male factor infertility. *Drugs*, 62:174153.

### Medical Treatment of Oligoasthenoteratozoospermia

12. O'Donovan P, Vandekerckhove P, Lilford R, et al. Treatment of male infertility: is it effective? Review and meta-analysis of published randomized controlled trials. *Hum Reprod* 1993;8:1209.
13. Reyes-Fuentes, A., Chavarria, M. E., Carrera, A., Aguilera, G., Rosado, A., Samojlik, E. et al: Alterations in pulsatile luteinizing hormone and follicle-stimulating hormone secretion in idiopathic oligoasthenospermic men: assessment by deconvolution analysis a clinical research center study. *J Clin Endocrinol Metab*, 81: 524, 1996.
14. Agarwal A, Sharma RK, Nallella KP, et al. 2006. Reactive oxygen species as an independent marker of male factor infertility. *Fertil Steril*, 86:87885.
15. Agarwal A, Prabakaran SA, Said TM. 2005. Prevention of oxidative stress injury to sperm. *J Androl*, 26:65460.
16. Chehval, M. J. and Mehan, D. J.: Chorionic gonadotropins in the treatment of the subfertile male. *Fertil Steril*, 31: 666, 1979.
17. Homonnai, Z. T., Peled, M. and Paz, G. F.: Changes in semen quality and fertility in response to endocrine treatment of subfertile men. *Gynecol Obstet Invest*, 9: 244, 1978.
18. Attia AM, Al-Inany HG, Proctor ML: Gonadotrophins for idiopathic male factor subfertility (update). *Cochrane Database Syst Rev* 2007;4:CD005071.
19. Allag, I. S. and Alexander, N. J.: Clomiphene citrate therapy for male infertility. *Urology*, 14: 500, 1979.
20. Bartsch, G. and Scheiber, K.: Tamoxifen treatment in oligozoospermia. *Eur Urol*, 7: 283, 1981.
21. A double-blind trial of clomiphene citrate for the treatment of idiopathic male infertility. World Health Organization. *Int J Androl*, 15: 299, 1992.
22. Vandekerckhove P, Lilford R, Vail A, Hughes E: Clomiphene or tamoxifen for idiopathic oligo/asthenospermia. *Cochrane Database Syst Rev* 2007;4:CD000151.
23. Raman JD, Schlegel PN. 2002. Aromatase inhibitors for male infertility. *J Urol*, 167:6249.
24. Clark, R. V. and Sherins, R. J.: Treatment of men with idiopathic oligozoospermic infertility using the aromatase inhibitor, testolactone. Results of a double-blinded, randomized, placebo-controlled trial with crossover. *J Androl*, 10: 240, 1989.
25. Lamensdorf, H., Compere, D. and Begley, G.: Testosterone rebound therapy in the treatment of male infertility. *Fertil Steril*, 26: 469, 1975.
26. Gerris J, Comhaire F, Hellemans P, Peeters K, Schoonajns F: Placebo-controlled trial of highdose mestrolone treatment of idiopathic male infertility. *Fertil Steril* 1991; 55: 603607.
27. Vandekerckhove, P., Lilford, R., Vail, A. and Hughes, E.: Androgens versus placebo or no treatment for idiopathic oligo/asthenospermia. *Cochrane Database Syst Rev*, 2: CD000150, 2000.
28. Costa, M., Canale, D., Filicori, M., D'Iddio, S. and Lenzi, A.: L-carnitine in idiopathic asthenozoospermia: a multicenter study. Italian Study Group on Carnitine and Male Infertility. *Andrologia*, 26: 155, 1994.
29. Lenzi A, Sgrò P, Salacone P, Paoli D, Gilio B, Lombardo F, Santulli M, Agarwal A, Gandini L: A placebo-controlled double-blind randomized trial of the use of combined L- carnitine and L-acetylcarnitine treatment in men with asthenozoospermia. *Fertil Steril* 2004; 81: 15781584.
30. Balercia G, Regoli F, Armeni T, Koverech A, Mantero F, Boscaro M: Placebo-controlled, double-blind, randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-Acetylcarnitine in men with idiopathic asthenozoospermia. *Fertil Steril* 2005; 84: 662671.
31. Balercia, G., Mosca, F., Mantero, F., Boscaro, M., Mancini, A., Ricciardo-Lamonica, G. et al: Coenzyme Q(10) supplementation in infertile men with idiopathic asthenozoospermia: an open, uncontrolled pilot study. *Fertil Steril*, 81: 93, 2004.
32. Comhaire FH, El Garem Y, Mahmoud A, Eertmans F, Schoonjans F: Combined conventional/ antioxidant Astaxanthin treatment for male infertility: a double-blind, randomized trial. *Asian J Androl* 2005; 7: 257262.
33. Adamopoulos DA, Pappa A, Billa E, Nicopoulou S, Koukkou E, Michopoulos J: Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertil Steril* 2003; 80: 914920.

**Dr. Sanjay Makwana**

MS, Dip. Pelvi. Surg. (Germany, France)  
Endoscopic Surgeon & Infertility Specialist  
Vasundhara Hospital & Fertility Research Centre, Rajasthan

Ovarian stimulation has long history, which goes back for more than 80 years. It started with the control of follicular growth- either to induce follicular growth in otherwise anovulatory cycles, or to induce multifollicular growth to increase the chances of conception.

In reality, and in the first instance, the full potential of the stimulated cycles was not achieved-mainly due to a single classical endocrine response. Multiple follicles, stimulated with hMG or clomiphene citrate with hMG, secrete estradiol to supranormal levels, attaining normal mid-cycle peak levels well in advance of the normal follicle size and maturity. The LH surge by the prematurely elevated estrogen concentrations leads to a confusing array of responses. Exposure of follicles to different degrees of maturity to the signal to luteinize and ovulate elicits a range of responses, and a broad range of follicles may be present when the surge occurs. Follicles which are capable of ovulation undergo luteinization and ovulation, while less mature follicle respond unconventionally to the LH surge, with inhibition of the aromatase enzyme, and granulosa cell mitosis, probably without ovulation. This process, recorded in non-ovulatory women as early as 1978.

In the 1980, the first reports were published on the use of gonadotropin-releasing hormone (GnRH) agonists. From then on, it was possible not only to control folliculogenesis but also to control pituitary function: to suppress endogenous luteinizing hormone (LH) for prevention of premature LH surge. This allowed, for the first time, an optimal timing of ovulation induction with human chorionic gonadotropins (hCG) and oocyte pick-up.

#### Gonadotropins

Human urinary preparations of LH and FSH (HMG) were used for ovarian stimulation in the early 1960's. The initial preparations were very impure with many contaminated proteins, with less than 5% of the proteins being bioactive. However, since the early 1980's, improved purification techniques have enabled the production of purified urinary FSH (uFSH) by the use of monoclonal antibodies.

The advent of recombinant DNA technology has enabled large-scale production of human recombinant FSH (rec-FSH). The technology allows for the transfection of human genes encoding for the common alpha (  $\alpha$  ) subunit and hormone specific beta (  $\beta$  ) subunit of glycoprotein hormone into Chinese hamster ovary cell lines, enabling large scale production of recFSH independent of the supply of human postmenopausal urine, and addressing concerns about batch to batch consistence's because of its purity, recFSH can now be administered by protein weight rather than bioactivity, and so called 'filled-by-mass' preparations with hMG(containing both LH and FSH bioactivity), followed by purified uFSH and more recently rFSH, rLH and rechCG. A new long acting FSH, corifollitropin alfa, has recently been introduced into clinical practice

#### GnRH analogs:

The pituitary down-regulation could be induced by the continued administration of GnRH. This induces an initial stimulation of gonadotropins release (the so called flare effect) followed by a down-regulation due to the clustering and internalization of the pituitary receptors. This resolved a number of issues associated with poor results related to hMG treatment alone, where a premature LH peak occurred in 20-25% of cycles due to the positive feedback activity by high serum  $E_2$  levels during the mid-follicular phase of the stimulation cycle. Induced pituitary down regulation resulted in a significant reduction in the cancelation rate and improved the overall IVF outcome in the 1980's.



GnRH antagonist were developed soon after, the low potency of the first two generations of drugs, and associated anaphylactic responses due to histamine release, delayed their clinical introduction until the third generation were shown to be safe and efficacious in IVF.

The immediate actions of GnRH antagonists mean that they can be administered during mid-to-late follicular phase to prevent premature luteinization. This avoids unpleasant 'menopausal' side effects associated with pituitary down regulation, and allows the endogenous inter-cycle FSH rise to be utilized for follicle stimulation. The cyclic recruitment and the initial stages of dominant follicle selection can proceed within the natural cycle and the use of exogenous FSH for inducing multiple follicle growth can be restricted to the mid to late follicular phase, as in certain mild stimulation protocols.

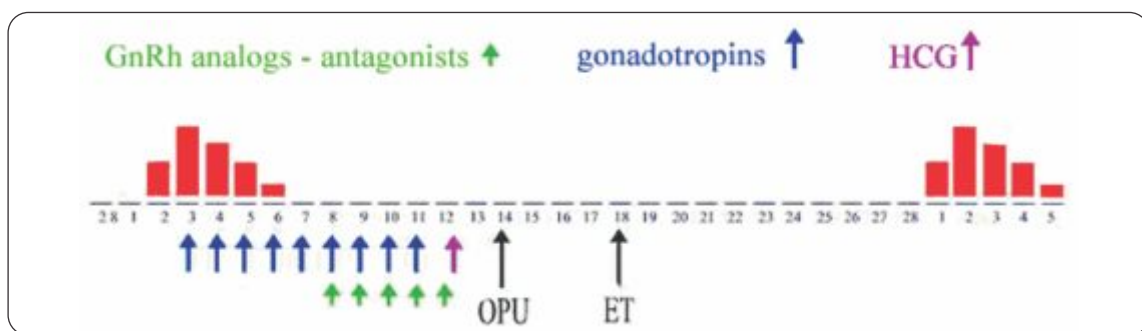


Fig: An Antagonist protocol for ovulation induction.

Current concepts: long protocol

The long ovarian stimulation protocol combining GnRH agonist with exogenous gonadotropin administration has been the most popular treatment regime. In the long protocol, GnRH agonist is usually administered during the luteal phase in the preceding cycle and is continued until hCG administration. In the short protocol GnRH agonist therapy is started on day 2 of the stimulation cycle, with the aim of utilizing the 'flare' effect of the GnRHa as an additional initial stimulus for follicular recruitment.

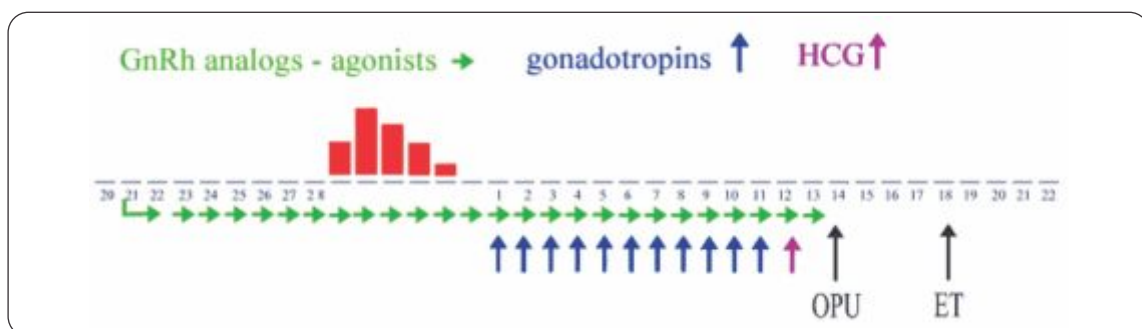


Fig: A traditional long protocol for ovulation induction.

Milder treatment regimes:

Traditional IVF stimulation regimes are associated with aggressive use of gonadotropins to stimulate the development of a large number of follicles. These traditional regimes are often complex, expensive extend over a prolonged period of time, and require intensive monitoring.

Increasing recognition of detrimental effects of conventional profound stimulation regimens has led to a change in the paradigm for ovarian stimulation in IVF.

Key to the development of milder stimulation protocols has been the introduction of GnRH antagonists which allow for the initiation of the IVF treatment cycle in a normal menstrual cycle with an undisturbed recruitment of a cohort of follicles during the early follicular phase. This approach enables the endogenous inter-cycle FSH rise to be utilized rather than suppressed, resulting in a reduction of gonadotropin required. The treatment cycles are thus shorter and not associated with hypoestrogenic side effects related to GnRH $\alpha$  down-regulation and reduced cancellation rates.

Milder regimes have been shown to produce proportionally more chromosomally normal embryos.

One of the most significant and high-risk side effects of ovarian stimulation is OHSS. Casting and cryopreservation are the two methods currently used to prevent OHSS. However, recently, cabergoline used in low doses for 8 days from the day of hCG administration was shown to reduce the rate of OHSS compared with placebo in a meta-analysis of four studies, the incidence but not the severity of OHSS was found to be reduced by cabergoline treatment without reducing pregnancy rates.

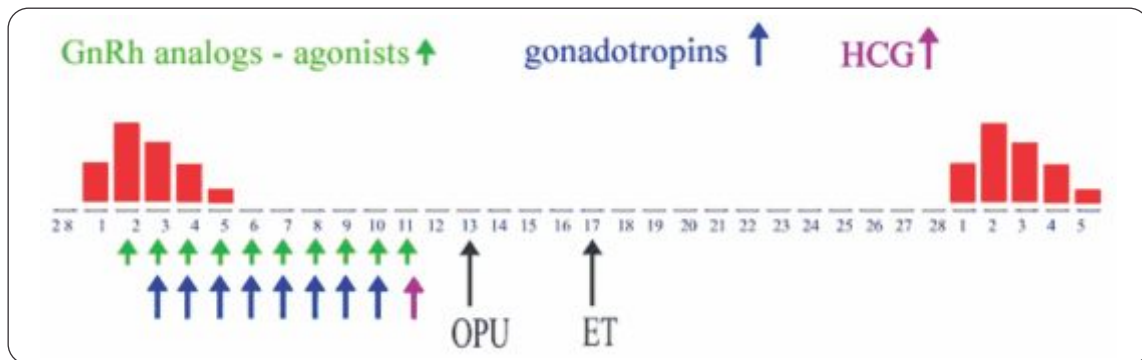


Fig: short protocol for ovulation induction.

A further development which promises to further reduce the burden of ovarian stimulation is the introduction of long acting FSH preparations which greatly reduces the number of injections required during an IVF treatment cycle. Corifollitropin alpha is a recombinant fusion protein composed of FSH and the carboxy terminal peptide (CPT) of the hCG beta-subunit which has a twofold extended time interval to peak serum concentration than recFSH preparations. This allows a single injection of Corifollitropin alpha to initiate and sustain multiple follicular growth for up to 7 days.

Role of adjuvant treatments:

Androgens are proposed to have a crucial role in steroid production within the ovary and keystone for effective hormonal control of ovulation, implantation and subsequent pregnancy. Androgens exert their effect on granulosa cells by regulating aromatase activity within the follicle. This enzyme converts androgen to estrogen, a vital controlling step in the recruitment and development of ovarian follicles.

DHEA (dehydroepiandrosterone) is an essential substrate and a prohormone for estrogen within the follicle. DHEA supplementation prior to ART stimulation in women with evidence of poor ovarian function may improve oocyte yield and embryo quality with increased spontaneous pregnancy rates.

Aromatase inhibitors (AIs) block aromatase activity within the follicle, inhibiting estrogen production. The advantage of using AIs is that they can reduce the negative feedback of the estradiol on the pituitary gonadotropin production, enhancing ovarian function without blocking estrogen receptors.

Metformin is an oral biguanide insulin-sensitizing agent that acts by inhibiting hepatic glucose production without causing hypoglycemia or increasing insulin production. By reducing insulin resistance and insulin levels

### Ovulation Induction

the hyperandrogenism is also regulated and associated with these agents. The elevated levels can also inhibit IGF-1 binding protein production by the liver, which can cause rise in follicular androgen production.

However, ultimately the most important criteria to judge the success or failure of treatment will be significantly associated with patient's experience. A mild stimulation regime with a GnRH antagonist regime has an equivalent live birth rate to a conventional IVF stimulation regime, and has advantages to tolerability and safety.

Looking into the future, ovarian stimulation in ART will progress into a new era where treatment will be more patient journey focused and holistic compared to the traditional IVF where success was defined to achieve pregnancy alone. In order to further improve outcomes focus should shift to optimize her health and factors known to influence outcome, prior to commencing therapy.

#### References

1. Wildt L, Hausler A, Marshall G, et al. frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. *Endocrinology* 1981;109:376-85.
2. Macklon NS, Fauser BC. Mild stimulation in in vitro fertilization. *Ann N Y Acad Sci* 2003;997:105-11.
3. Hohmann FP, Macklon NS, Fauser BC. A randomized comparison of two ovarian stimulation with gonadotropin-releasing hormone(GnRH) antagonist cotreatment for in-vitro fertilization commencing recombinant follicle-stimulation hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol. *J Clin Endocrinol Metab* 2003;88:166-73.
4. Alvarez C, Marti-Bonmati L, novella-Maestre E, et al. dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulaetd women undergoing assisted reproduction. *J Clin Endocrinol Metab* 2007;92:2931-7.
5. Youssef MA, van Wely M, Hassan MA, et al. Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systemetic review and meta-analysis. *Hum Reprod Update* 2010;16:459-66.
6. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995;49:721-49.
7. Massin N, Cedrin-Durnerin I, Coussieu C, et al. Effects of transdermal testosterone application on the ovaraian response to FSH in poor responders undergoing assisted reprocdution technique- a prospective, randomized, double-blind study. *Hum Reprod* 2006;21:629-34.