Management of anovulatory infertility

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ABSTRACT

Anovulatory subfertility is a heterogeneous condition with various underlying causes, which should be identified with appropriate history taking, physical examination and relevant investigations. Optimisation of body weight is essential in either underweight or overweight/obese individuals. Patients with hypogonadotrophic anovulation can be treated with pulsatile GnRH therapy or a gonadotrophin preparation containing both FSH and LH activities. For normogonadotrophic anovulation, clomiphene citrate should be used as the first-line medical treatment. Metformin co-treatment with clomiphene citrate may be considered in a subgroup of patients with polycystic ovary syndrome who are obese or clomiphene-resistant. Ovulation induction with gonadotrophin or laparoscopic ovarian drilling is the next option. Dopamine agonist is indicated for anovulation due to hyperprolactinaemia.

INTRODUCTION

Ovulation disorders account for the cause in about 15-20% of patients seeking treatment for subfertility [1] and can be classified according to the site of deficiency in the hypothalamic-pituitary-ovarian axis (Table 1) as in the World Health Organisation (WHO) classification [2].

Table 1: Classification of ovulation disorders

1. Hypogonadotrophin hypogonadism (WHO group I)

    - Idiopathic hypogonadotrophic hypogonadism

    - Kallmann's syndrome (isolated gonadotrophin deficiency and anosmia)

    - Functional hypothalamal dysfunction (e.g. excessive weight loss such as in anorexia nervosa, exercise, stress, drugs, iatrogenic)

    - Pituitary tumour, pituitary infarct (e.g. Sheehan's syndrome)

2. Normogonadotrophic normogonadic ovarian dysfunction (WHO group II)

    - Polycystic ovary syndrome (PCOS)

3. Hypergonadotrophic hypogonadism (ovarian failure) (WHO group III)

    - Genetic (e.g. Turner's syndrome)

    - Autoimmune causes

    - Infection (e.g. mumps oophoritis)

- Iatrogenic (e.g. surgical menopause, post-radiotherapy or chemotherapy)

- Idiopathic

4. Other endocrinopathies: e.g. hyperprolactinaemia, thyroid dysfunction, other conditions of androgen excess such as congenital adrenal hyperplasia and androgen-secreting adrenal/ovarian tumours

INITIAL ASSESSMENT AND INVESTIGATIONS (Figure 1)

History and physical examination:

Anovulatory women typically present with oligomenorrhoea or amenorrhoea, although about 10% of women with regular menstrual cycles could be anovulatory. A detailed menstrual history needs to be taken, including the cycle length, regularity and the last menstrual period. Symptoms associated with hyperprolactinaemia (galactorrhoea, headache, visual disturbance), thyroid dysfunction and climacteric symptoms should be enquired as well, in addition to any related drug or medical history which might have precipitated the menstrual cycle disturbance. Hyperandrogenic symptoms, such as hirsutism, acne, greasy skin, and male pattern alopecia may be evident in polycystic ovary syndrome (PCOS) or other disorders of androgen excess. Other relevant history would include any recent weight changes, diet, stress and exercise pattern, as well as history of secondary sexual development.

In examination, stigmata of chromosomal abnormalities, secondary sexual development, body mass index, signs of hyperandrogenism, galactorrhoea and goitre, as well as abnormal genital development should all be noted.

Investigations:

A mid-luteal phase serum progesterone test is the recommended investigation for assessment of ovulation status, and a level of 30 nmol/l or above confirms presence of ovulation. It is preferably taken about 7 days before the next menstrual period, and the correctness of the timing can be assessed by noting the menstrual date following the blood test. Borderline levels (15-30 nmol/l) are usually due to mis-timed blood taking and, a repeat test may help confirmation.   Basal body temperature charts and urine LH assays are less robust investigations and subject to greater variations; these are not recommended for determination of ovulation.

A blood test for serum follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) and prolactin are the basic work-up for oligoamenorrhoea who are presumed to be anovulatory.   A progestogen challenge test would offer a functional test of the oestrogenic status.   Androgen profile may be checked although there is no universal consensus for defining biochemical hyperandrogenism and reference ranges vary between laboratories. In case of severe hyperandrogenaemia (e.g. total testosterone >5 nmol/l) [3] or signs of severe hirsutism or virilisation, it needs to be followed by checking 17-hydroxyprogesterone to exclude late-onset congenital adrenal hyperplasia, an overnight dexamethasone suppression test to exclude Cushing's syndrome, as well as appropriate imaging (ultrasound

scan of the pelvis and CT scan of the adrenals) to exclude an androgen-secreting tumour.

In the Rotterdam criteria, ultrasonographic feature of polycystic ovaries is one of the diagnostic criteria for PCOS. Polycystic ovary morphology is defined as either 12 or more follicles measuring 2 to 9 mm in diameter, and/or increased ovarian volume (>10 ml); only one ovary fitting this definition is sufficient for the definition [4]. If there is a dominant follicle (>10 mm) or a corpus luteum, a repeat scan in the next cycle should be done. LH:FSH ratio is no longer regarded as a diagnostic criteria for PCOS due to the large variations.

Before managing anovulatory subfertility, semen analysis of the male partner should be performed to exclude severe male factors which would alter the choice of treatment. Unless tubo-peritoneal factor is suggested by history, simple oral medical treatment for ovulation induction can be commenced without tubal assessment.

TREATMENT PRINCIPLES FOR THE COMMON CAUSES

Hypogonadotrophic hypogonadism (WHO group I):

This may be manifested as primary or secondary oligo-amenorrhoea. Serum FSH, LH and oestradiol levels are typically low although the degree may vary and is sometimes not clearly

distinguishable from WHO group II anovulation.   If there is a treatable cause, treatment should be directed to the cause. Surgery may be indicated in cases of intracranial tumours. Patients with anorexia nervosa may benefit from psychotherapy and weight gain after extensive counselling. Ovulation can be induced by pulsatile GnRH administration (for hypothalamic but not pituitary causes) or gonadotrophins (containing both FSH and LH) [5] if anovulation persists despite optimization of body weight.

Normogonadotrophic anovulation (WHO group II):

PCOS accounts for the majority of these patients, although the typical full-blown picture may not be present in some cases. Other causes of androgen excess may also contribute to this picture. Weight reduction should be the first-line treatment in obese PCOS women, and this may result in resumption of spontaneous ovulation and also improve their response to ovulation induction if indicated.   Ovulation induction can be achieved with clomiphene citrate (CC) or aromatase inhibitors.   Those not responsive to or failing oral treatment may be offered gonadotrophins or ovarian drilling.   Other causes of androgen excess should be managed accordingly.

Hypergonadotrophic hypogonadism (WHO group III)

These women may present with primary or secondary amenorrhea with elevated FSH and

low oestradiol levels. Ovarian biopsy for detecting the presence of follicles in case of resistant ovary syndrome is not recommended because of the invasive nature and doubtful value of the procedure [6,7]. About half of young women with ovarian failure may have intermittent and unpredictable ovulation, and spontaneous pregnancies have been reported in approximately 5–10% of cases subsequent to the diagnosis [8]. However, any form of ovulation induction treatment is not advisable in these women. The only realistic option is assisted reproduction using donor eggs.

Hyperprolactinaemia

Hyperprolactinaemia interferes with the pulsatile secretion of GnRH and impairs normal ovarian function. Causes of hyperprolactinaemia include prolactin-producing adenoma, other pituitary tumours which block the inhibitory signal of the hypothalamus, primary hypothyroidism, chronic renal failure, and drugs such as neuroleptics and calcium channel blockers.

Conditions of falsely high prolactin levels should be noted so as to avoid unnecessary interventions. Transiently raised prolactin level can be triggered by breast examination and stress, for instance due to venepuncture. Macroprolactinaemia can also be a cause of pseudohyperprolactinaemia. Macroprolactin are high molecular weight polymers of

prolactin molecules which are biologically inactive. It can be differentiated by polyethylene glycol study [9].

Asymptomatic patients with hyperprolactinaemia can be observed without treatment. In anovulatory women with hyperprolactinaemia, dopamine agonist is the first-line treatment to lower the prolactin level and shrink the prolactinoma if present. The risk of tumour expansion with neurological sequelae is rare with microadenoma (<10 mm). Women with macroprolactinoma (>10 mm) may be managed with the neurosurgeon's input, and they should conceive after normalization of serum prolactin and significant reduction of tumour volume so as to reduce the neurological risk of optic chiasm compression during pregnancy [10]. Surgical treatment by transphenoidal pituitary adenectomy and rarely radiotherapy may be required if medical treatment fails to shrink a macroadenoma.

WEIGHT MANAGEMENT AS A THERAPEUTIC OPTION

Weight gain in underweight women

Undernutrition and underweight can exert an inhibitory effect on the hypothalamo-pituitary-ovarian axis thereby suppressing ovulation. Although underweight does not seem to adversely affect the pregnancy rate in fertility treatment, underweight or malnourished women who conceive have higher risks of obstetric complications like

hyperemesis gravidarum, anaemia, fetal growth restriction and premature delivery. Therefore, women with eating disorders should be advised to postpone conception until remission and normalization of body weight. Nutritional counselling should be offered [11].

Weight reduction in overweight and obese women

Both overweight and obese women are associated with a higher incidence of menstrual disturbance, ovulation disorders and subfertility in women [12]. They have poorer response to ovulation induction [13] and a higher risk of pregnancy complications such as miscarriage, gestational diabetes, hypertension, fetal macrosomia and intrapartum problems [11,14-16].

Weight loss should be advised prior to fertility treatment in overweight and obese women. Even a modest weight loss of 5% may restore spontaneous ovulation and possibly improve pregnancy rate [17,18]. There is limited data on its effect on pregnancy complications. Weight loss should be achieved with lifestyle modification by caloric restriction and increased physical exercise. Reduced caloric intake by 500-1000 kcal/day has been suggested to be effective, aiming at reducing the body weight by 7-10% over a period of 6-12 months. Structured moderate exercise lasting for 30 minutes or more per day is advisable [18]. In individuals who experience difficulty in reducing significant weight with

lifestyle intervention alone, the use of anti-obesity drugs can be an adjunct. Orlistat and metformin are the options currently, and their use is probably safe for women planning for pregnancy. Bariatric surgery can be an option for refractory cases. [15,16,19]

The effects of caloric restriction, excessive physical exertion or pharmacological intervention in the periconceptional period are not yet known, and hence those interventions should precede any planned pregnancy or fertility treatment [17].

MEDICAL OPTIONS FOR OVULATION INDUCTION

Dopamine agonists

The dopamine agonists (bromocriptine, carbergoline and quinagolide) inhibit prolactin secretion from the pituitary lactotrophs, leading to restoration of gonadal function and shrinkage of prolactinoma. Bromocriptine is given at a daily dosage of 2.5 to 20 mg in divided doses 2-3 times a day. Cabergoline and quinagolide have longer biological half lives than bromocriptine. Cabergoline is administered once or twice weekly and quinagolide once daily. Response can be monitored by menstrual pattern and serum prolactin levels.

Dopamine agonist therapy restores ovulation in about 90% of women with anovulation

related to hyperprolactinaemia. Cabergoline [20] and quinagolide [21,22] are more effective than bromocriptine in restoring normal prolactin concentrations and ovulatory cycles. In patients who do not ovulate even when prolactin concentrations are within normal range, dopamine agonists can be combined with anti-oestrogen or gonadotrophin as appropriate.

Common side effects with bromocriptine include nausea, vomiting, abdominal cramps, vertigo, postural hypotension, headaches and drowsiness. Around 12% of patients discontinue the treatment for this reason. This can be minimised by gradual step up from a low starting dose and taking the drug at bedtime, or by administering vaginal bromocriptine. Significantly lesser side effects were reported in patients taking cabergoline and quinagolide when compared with bromocriptine. [23]

Dopamine agonists have not been associated with any adverse effect on pregnancy or fetal development [23], although we commonly recommend patients with microprolactinomas or idiopathic hyperprolactinaemia to stop treatment once pregnancy is confirmed in order to avoid any potential harm. Therapy may be continued during pregnancy in cases of macroprolactinoma or where there is evidence of tumour expansion [10,24].

The European Medicines Agency has issued warnings on the risk of cardiac valvular fibrosis associated with cabergoline which were reported mostly with long-term use in high doses [25]. Bromocriptine and quinagolide have weaker affinity for the 5HT-2B receptor and are hence thought to be less valvulopathic, although little data is available especially with the low-dose use for treatment of hyperprolactinaemia [26].

Anti-oestrogens

1. Clomiphene citrate (CC):

CC is commonly used as the first line drug in treatment of WHO group II anovulation. It is an orally active non-steroidal compound which acts primarily by its anti-oestrogenic property. It displaces endogenous oestrogen from oestrogen receptors in the hypothalamic-pituitary axis, diminishing its negative feedback and hence increasing the secretion of endogenous GnRH and gonadotrophins which subsequently induce ovulation.

It should be started at 50 mg daily for five days following a spontaneous or progestogen-induced withdrawal bleeding. The recommended maximum dose is 150 mg per day as there was no clear evidence of efficacy at higher doses [17]. Commencement from any day between day 2 to 5 produced the same results [27]. Ovulation usually occurs within 5-10 days after the last tablet. If there is no ovulation, the dose can be stepped up at

increments of 50 mg daily until ovulation occurs, or a maximum dose of 150 mg daily is reached.

It is recommended to monitor the response at least during the first treatment cycle [28]. Follicular tracking by transvaginal pelvic ultrasound helps to identify non-response, excessive response or reduced endometrial thickness. Ovulation can be confirmed by checking serum progesterone in the mid-luteal phase.

Treatment with CC can achieve ovulation, pregnancy and live birth rates of 73%, 36% and 29% per patient respectively [29]. Treatment should generally be limited to six ovulatory cycles [29], but further treatment up to 12 cycles may be considered on an individual basis. Patients who are resistant to maximum dose of CC or who fail to conceive after 6 ovulatory cycles of CC treatment should be offered second-line treatment.

Two RCTs [30,31] showed no significant difference in pregnancy rate with hCG administration or not, nor in the incidence of miscarriage or multiple pregnancy. Therefore, the use of hCG trigger is not routinely needed except in patients where failure of follicular rupture is evident.

CC is generally very well tolerated, although side effects including hot flushes, breast discomfort, abdominal distension, nausea, vomiting, nervousness, mood swings, dizziness, hair loss and disturbed vision may be occasionally encountered. Approximately 7-10% of CC-induced pregnancies are twins and 0.5-1% are triplets [32]. While mild ovarian enlargement is relatively common, severe OHSS is very rare. There is no increase in spontaneous abortion or congenital abnormalities in CC-induced pregnancies.

2. Tamoxifen

Tamoxifen is a triphenylethylene derivative which is structurally similar to CC. The suggested dose in ovulation induction is 20-40 mg daily for 5 days after a spontaneous period or withdrawal bleed. A meta-analysis [33] reported that tamoxifen and CC had similar ovulation rates and pregnancy rate per cycle. It should be noted that the use of tamoxifen for ovulation induction is an off-label use, despite the available evidence on its efficacy and safety for such indication.

Insulin sensitising agents

In women with PCOS, insulin resistance is one recognised metabolic disturbance. Insulin-sensitising agents can increase the insulin responsiveness in target tissues, reduce the compensatory hyperinsulinaemia and hence ameliorating its adverse effect on ovulatory

function. Metformin, a biguanide, is one of the most commonly used insulin sensitiser and can be given at 500 mg tds or 850 mg bd with meals. Gastrointestinal upset including nausea, vomiting, diarrhoea are the most common side effects. Lactic acidosis is a rare though serious complication, and hence it is contraindicated in patients with renal, hepatic or major cardiovascular disease or hypoxia.

As reported in a Cochrane review [34], metformin used alone improves the ovulation rate (OR 2.12; 95% CI 1.5–3.0) and clinical pregnancy rate (OR 3.86; 95% CI 2.18–6.84) compared with placebo or no treatment, but not the livebirth rate (OR 1.0; 95% CI 0.16–6.39). When compared with CC, metformin leads to lower ovulation rate (OR 0.48; 95% CI 0.41–0.57) and clinical pregnancy rate (OR 0.63; 95% CI 0.43–0.92), and a non-significant trend of lower livebirth rate (OR 0.67; 95% CI 0.44–1.02). Co-treatment with metformin and CC improves the ovulation rate (OR 1.76; 95% CI 1.51–2.06) and clinical pregnancy rate (OR 1.48; 95% CI 1.12–1.95), but not the livebirth rate (OR 1.05; 95% CI 0.75–1.47) compared with CC alone.

Previous subgroup meta-analyses showed a higher clinical pregnancy rate after metformin plus CC co-treatment compared with CC alone in obese patients only but not in non-obese patients, and in CC-resistant subjects only [35]. Another systematic review [36] also

suggested that metformin plus CC gave to higher livebirth rates than CC alone only in CC-resistant women but not in CC-naïve women.

There has not been good evidence to support the safe and effective use of other insulin sensitizers in fertility treatment.

Aromatase inhibitors

Aromatase catalyses the conversion of androstenedione and testosterone to oestrone and oestradiol respectively. Aromatase inhibitors block the production of oestrogen, reducing the negative feedback to the hypothalamic-pituitary axis, hence increasing endogenous FSH secretion. They have been used for many years as an adjunctive treatment for breast cancer and are gaining in popularity for ovulation induction in patients with PCOS.

Letrozole is the third-generation aromatase inhibitor most commonly used for ovulation induction. When compared with CC, letrozole has a much shorter half life and hence minimal suppressive effect on the endometrium. The recommended regimen is 2.5 to 5 mg per day for five days commencing in the first 5 days of spontaneous or induced bleeding [37], or as a single dose of 20 mg on day 3 of the period [38]. The monitoring is similar to that of CC. It should be noted that the use in ovulation induction is an off-label use.

Letrozole gave an ovulation rate of 70–84% and a pregnancy rate of 20–27% per cycle in CC-resistant women with PCOS [39]. A meta-analysis [40] showed no significant difference between letrozole and CC in the ovulation rate, pregnancy rate per cycle or per patient.

Letrozole is generally well tolerated. Earlier reports suggested that letrozole results in more monofollicular development and significantly lower multiple pregnancy rate compared with CC. However, in a recent RCT [41], it had comparable chance of twin pregnancies as CC (8.3% vs 9.1%). There was also a case report of a triplet pregnancy following ovulation induction with letrozole [42].

Teratogenic effects of letrozole have been described in animal studies [43,44]. An abstract report [45] suggested that the use of letrozole for subfertility treatment might be associated with a higher risk of congenital cardiac and bone malformations in the newborns. A retrospective study with a much larger sample size could not show any difference in the overall rates of major and minor congenital malformations among newborns from mothers who conceived after letrozole or CC treatments [46].

Gonadotrophin-releasing hormone (GnRH)

GnRH administered in a pulsatile fashion restores the normal pattern of gonadotrophin secretion as in spontaneous menstrual cycles, leading to the development of a single dominant follicle. It is indicated for treatment of hypogonadotrophic anovulation due to hypothalamic dysfunction but not pituitary problem. It is administered by the subcutaneous or intravenous route through a small butterfly cannula using a small battery-operated pump.

Cumulative pregnancy rates of 80% and 93% have been reported after 6 and 12 cycles of treatment respectively [47]. Multiple pregnancy rates ranged between 3.8-13.5% [48-50]. Other drawbacks include the inconvenience of having the needle in situ for long period, needle site reaction and infection, displacement and pump failure, and its relatively high cost.

Gonadotrophin

The use of exogenous gonadotrophins is to overcome the FSH threshold required for follicular development. FSH is the key gonadotrophic hormone for follicular development. However, in women with hypogonadotropic hypogonadism a preparation containing both FSH and LH gives better outcome than purely FSH [51] because LH is required for ovarian

steroidogenesis to achieve optimal endometrial proliferation. In these women, luteal phase support is necessary.

(a) Chronic low-dose, step up protocol

This is currently the recommended protocol in many centres worldwide. The principle is to determine the FSH threshold gradually, avoiding excessive stimulation and multifollicular development. FSH is commenced at a low starting dose (37.5-75 IU/day) for at least 10-14 days [17] and stepped up at weekly intervals by increments of 37.5 IU up to a maximum of 225 IU/day if there is no response. The same dose is maintained once follicular growth is observed. Once 1 to 2 dominant follicles reach 18 mm in mean diameter, hCG is administered to trigger ovulation. It may take up to several weeks to achieve an ovarian response in the first treatment cycle in women with a high FSH threshold. In subsequent cycles, FSH can be started at a dose that gives rise to ovarian response in the first cycle.

(b) Step down protocol

This protocol mimics the physiological hormonal cycle. Gonadotrophin injection is commenced at a daily dose of 150 IU starting from day 2-3 of the cycle and the ovarian response is monitored by ultrasound every 2-3 days. The same dose is continued until a dominant follicle reaches 10 mm, which is then reduced to 112.5 IU/day for 3 days and then

further down to 75 IU/day until hCG is administered to trigger ovulation. It requires more intense monitoring than the step up protocol.   The step down regimen has a shorter duration of stimulation compared to the step up protocol, but a higher rate of multifollicular development and ovarian hyperstimulation syndrome, as well as a lower ovulation rate. The pregnancy rate is comparable between the two regimens [52].

Ovulation induction with low-dose gonadotrophin regimens has monofollicular ovulation rate and pregnancy rates of about 70% and 20% respectively, and a cumulative pregnancy rate of 55-70%.   The rates of ovarian hyperstimulation syndrome and multiple pregnancy are as low as <1% and 6% respectively.   Such results are superior to conventional dose gonadotrophin regimens which gave significantly higher risk of multiple pregnancy and severe ovarian hyperstimulation syndrome. [17]

Adverse effects include ovarian hyperstimulation syndrome and multiple pregnancy.   It is mandatory to exercise vigilant monitoring with adjustment of the gonadotrophin dosage as appropriate. Cycles with more than 2 dominant follicles should be cancelled and the starting dose should be reduced in subsequent cycles.

A recent randomized trial suggested that when low-dose FSH was used as the first-line

treatment in treatment-naïve women with PCOS, the reproductive outcome was significantly better than with CC, with respect to live birth rate per first cycle, cumulative live birth rate over three cycles and time to pregnancy [53].   Further studies on the cost-effectiveness of such approach are warranted, and the choice between the two modalities of treatment would be subject to the individual clinic setting and resources and the patient's preference.

Risk of ovarian cancer with ovulation inducing agents

There have been concerns over the risk of ovarian malignancy following ovulation induction. A cohort study [54] indicated a RR of 11.1 (95% CI 1.5-82) with long term use of CC over 12 months.   A collaborative analysis [55] also showed an increased risk (OR 2.8; 95% CI 1.3-6.1) of invasive ovarian cancer in subfertile women who had used fertility drugs compared to fertile women.   A meta-analysis [56] showed a significantly higher risk of ovarian cancer in subjects exposed to fertility drugs when compared with general population controls (OR 1.52; 95% CI 1.18-1.97), but not when compared with subfertile controls not exposed to fertility drugs. Indeed, treated infertile patients had a tendency towards a lower incidence of ovarian cancer (OR 0.67; 95% CI 0.32-1.41) compared with untreated subfertile patients. It suggested that subfertility itself rather than the use of fertility drugs is the risk factor for developing ovarian cancer.   Another recent large cohort study [57] in the Danish

population reported a 46% higher risk of ovarian cancer in women attending the subfertility clinic compared to the general population after adjustment for parity. However, the overall risk of ovarian cancer was not significantly affected by the use of fertility drugs including CC, GnRH and gonadotrophins.   Overall, findings to date on ovarian cancer risk associated with fertility drug treatment seemed reassuring though not definitive.

SURGICAL INDUCTION OF OVULATION

In patients with clomiphene resistance or failure, ovarian drilling can be an option. Laparoscopic ovarian drilling (LOD) is the preferred surgical method of ovulation induction over conventional ovarian wedge resection by laparotomy, as the latter is associated with a higher risk of postoperative adhesion formation. The mechanism of action of LOD is unclear, but may be related to the destruction of androgen-producing tissue in the ovary.

One commonly adopted regimen of LOD makes use of the monopolar electrocautery needle to make four punctures (7-8 mm in depth) per ovary at a 30W power for 5 seconds per puncture [58,59]. Alternatively, laser vaporisation can be performed using carbon dioxide, argon or Nd:YAG crystal lasers.

LOD is not superior to CC as a first-line method of ovulation induction in women with

PCOS [60].   In a Cochrane review [61], the livebirth rate of LOD is comparable to gonadotrophins, with the pooled OR being 1.04 (95%CI 0.59 to 1.83), and no difference in miscarriage rate. The multiple pregnancy rate was lower, and no OHSS was reported, with LOD in contrast to gonadotrophin.   LOD as a first-line treatment produces an ovulation rate of 64% in PCOS women [60], and in CC-resistant PCOS women it gives a pregnancy rate of 67% [59].   About 50% of patients may need post-operative adjuvants.   CC and gonadotrophins can be considered after 3 and 6 months if the woman is still anovulatory.

Compared to gonadotrophin treatment, LOD is less costly, provides laparoscopic tubal/pelvic assessment with the possibility of therapeutic surgery concurrently if indicated, allows multiple attempts of conception, and can achieve monofollicular ovulation without the need for intensive monitoring.   The main drawback of LOD is the small anaesthetic and surgical risk, possibility of adhesion formation and damage to ovarian reserve.

SUMMARY

Anovulation subfertility can be due to a multitude of underlying causes, which should be identified with appropriate history taking, physical examination and relevant investigations. Optimisation of body weight is essential in either underweight or overweight/obese individuals. Women with hypogonadotrophic, normogonadotrophic and hyperprolactinaemic anovulation can be offered the appropriate medical and/or surgical treatment option based on the exact diagnosis and treatment history. Treatment with donor oocyte is the only option in women with ovarian failure.

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