

Guideline on Induction of Ovulation

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1 PURPOSE AND SCORE

This guideline covers the classification of ovulation disorders, treatment options of various ovulation disorders and their associated risks.

2 INTRODUCTION

Ovulation disorders account for 20% of the causes of subfertility (1). The goal of ovulation induction is to achieve development of a single follicle and subsequent ovulation in women with anovulation. The selection of the most appropriate treatment for ovulation disorders depends upon reaching the correct diagnosis. Patients should be fully informed of the treatment options available, the success of each treatment option and the associated risks.

3 CLASSIFICATION

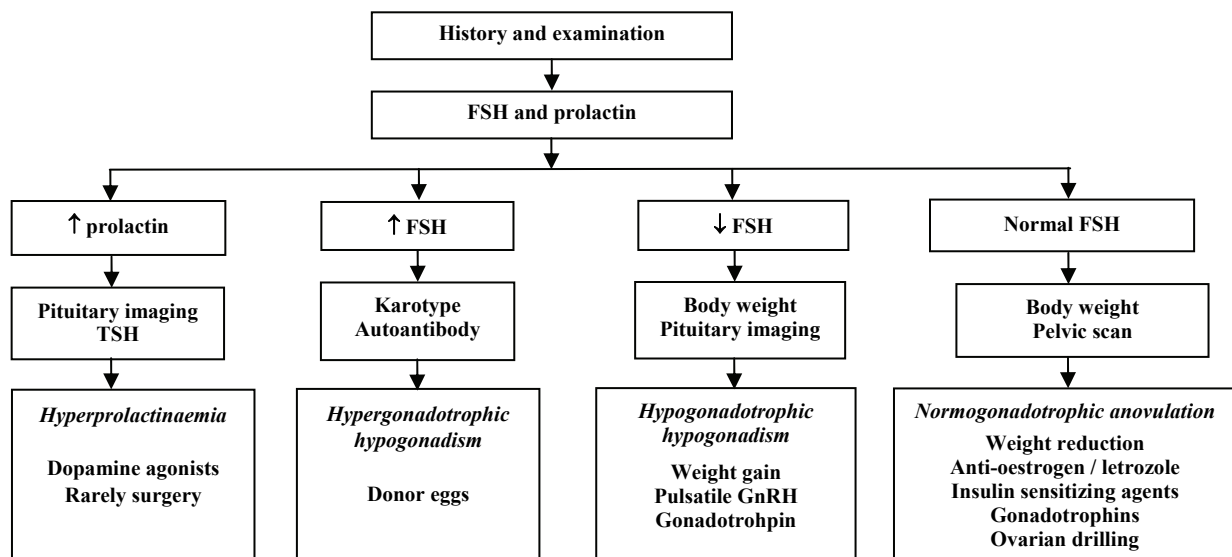
Ovulation disorders can be classified according to the anatomical site where the hypothalamic-pituitary-ovarian axis is

deficient (Table 1). The corresponding World Health Organisation (WHO) classification (2) is also given for reference.

Table 1: Classification of ovulation disorders

1. Intrinsic ovarian failure (WHO group III)
 - genetic, autoimmune, following chemotherapy or radiotherapy
2. Secondary ovarian dysfunction
 - a) Disorders of gonadotrophin regulation
 - i) Specific
 - hyperprolactinaemia
 - Kallmann's syndrome (WHO group I)
 - ii) Functional (WHO group I)
 - weight loss, exercise, drugs, idiopathic
 - b) Gonadotrophin deficiency (WHO group I)
 - pituitary tumour, pituitary necrosis or thrombosis
 - c) Disorders of gonadotrophin action (WHO group II)
 - Polycystic ovary syndrome (PCOS)

Figure 1: Flowchart of diagnosis and treatment



Adequate history and physical examination are essential. Further investigations are necessary to pinpoint where the defect in the hypothalamic-pituitary-ovarian axis is occurring. Based on the results of the investigation, the causes of anovulation can be divided into four distinct categories (3).

3.1 Hyperprolactinaemia

Hyperprolactinaemia can be found in 15% of women with anovulation, and in 75% of women with both anovulation and galactorrhoea (4). It interferes with the pulsatile secretion of GnRH and impairs normal ovarian function. Causes of hyperprolactinaemia include a prolactin-producing adenoma, other tumours of the pituitary region blocking the inhibitory control of the hypothalamus, primary hypothyroidism, chronic renal failure, and a variety of drugs.

Prolactin molecules form irregular high molecular weight polymers to produce a biologically inactive form called 'macroprolactin'. Macroprolactinaemia has no clinical significance and does not require any treatment. It should be considered in patients with no apparent hyperprolactinaemic symptoms (5). The correct diagnosis can be made using prolactin chromatography and polyethylene glycol immunoprecipitation. It has been suggested that routine screening for macroprolactin in sera from subjects with suspected hyperprolactinaemia is cost-effective and should be performed to prevent inaccurate diagnosis and unnecessary intervention for hyperprolactinaemia (6).

Asymptomatic patients with hyperprolactinaemia may not require treatment, and periodic observation should then suffice. When a woman with a macroprolactinoma wishes to become pregnant, it is necessary to plan conception to occur after serum prolactin is normalized and the tumour volume is significantly reduced in order to avoid or reduce the risk of compression of the optic chiasm during pregnancy (7).

The first-line treatment is the use of dopamine agonists which lower prolactin concentration and cause shrinkage of a prolactinoma if present. Surgery in the form of trans-sphenoidal pituitary adenomectomy is seldom

indicated in the presence of a prolactinoma because of high recurrence rate and possibility of panhypopituitarism (8-9). Radiotherapy is used very infrequently and is considered only if both medical and surgical treatments fail or are contraindicated.

3.2 Hypergonadotrophic hypogonadism (WHO group III)

Hypergonadotrophic hypogonadism or ovarian failure may be due to chromosomal abnormalities, autoimmune disorders, infection (mumps oophoritis), and irradiation or cytotoxic drugs. Many cases, however, are idiopathic even after extensive investigations. These women present with primary or secondary amenorrhea with low endogenous oestrogen and highly elevated FSH levels. There is no advantage in performing laparoscopy and ovarian biopsy to detect the presence of follicles in the resistant ovary syndrome because of the invasive nature and the doubtful value of the procedure (10-11).

About half of young women with spontaneous hypergonadotrophic hypogonadism experience intermittent and unpredictable ovarian function and spontaneous pregnancies have been reported in approximately 5–10% of cases subsequent to the diagnosis (12). Although there have been case reports of successful ovulation induction treatment, any form of ovulation induction is not advisable in these women. The only realistic treatment for these patients is the use of donor eggs in an in vitro fertilisation setting. In addition, they should be offered longterm hormone replacement therapy to protect their bones from the deleterious effects of hypo-oestrogenism.

3.3 Hypogonadotrophic hypogonadism (WHO group I)

These patients present with primary or secondary amenorrhoea. They have very low serum oestradiol concentration due to low FSH and LH secretion from the pituitary gland (hypogonadotrophic hypogonadism). It can be due to either congenital causes such as Kallmann's syndrome (isolated gonadotrophin deficiency and anosmia) or acquired causes such as pituitary tumour, pituitary necrosis (Sheehan's syndrome), stress and excessive weight loss (anorexia nervosa).

Surgery is clearly indicated in patients with central nervous system tumours. Patients with anorexia nervosa may benefit from psychotherapy and weight gain after extensive counselling. Pulsatile GnRH or gonadotrophins containing both FSH and LH (13) is offered to patients with other hypogonadotrophic causes or with persisting anovulation despite weight gain.

3.4 Normogonadotrophic anovulation (WHO group II)

This includes a heterogeneous group of patients who can present either with regular cycles, oligomenorrhoea, or even amenorrhoea. The midluteal serum progesterone is low, FSH levels are in the normal range and prolactin is normal. Most of these patients are likely to have PCOS. Other causes include congenital adrenal hyperplasia, adrenal tumours, and androgen-producing ovarian tumours. In these conditions, the patient may have clinical symptoms or signs of hyperandrogenism such as hirsutism, which should require more detailed investigations such as measurement of dehydroepiandrosterone sulphate and 17-OH progesterone.

Obese PCOS women will benefit from weight loss, as this might lead to resumption of spontaneous periods and ovulation and will also improve their response to ovulation induction. They usually respond well to clomiphene citrate (CC) or aromatase inhibitors, failing that, to gonadotrophins for ovulation induction. Insulin sensitising agents or laparoscopic ovarian drilling may be considered in those not responding to CC. Specific causes, such as adrenal or ovarian tumours, should be treated by removing the cause. Congenital adrenal hyperplasia benefits from corticosteroid therapy.

4 TREATMENT

Effective use of ovulation induction agents requires understanding of their mechanism of action, proper indications, different regimens, monitoring methods, and potential complications.

4.1 Weight reduction

Body mass index (BMI) is more representative of body fat and is calculated

from weight in kg/height squared in m. Overweight is defined as BMI ≥ 25 kg/m² and obesity is BMI ≥ 30 kg/m² (14). Overweight and obese women have a higher incidence of menstrual disturbance, ovulation disorders and subfertility (15). They may require higher dosage of ovulation drugs to achieve successful ovulation but have lower ovulation rates and delayed responses to various treatments of ovulation induction, if needed.

Ovulation induction with CC in overweight and obese women results in lower ovulation rates (16) and lower cumulative live birth rates for women with a BMI >30 kg/m² (17). The dose of CC required to achieve ovulation is positively correlated with body weight (18). Ovulation rates following gonadotrophin therapy in overweight women are lower due to higher cancellation rates (19-20) but this decreased success rate is not found in all studies (21). Women with BMI of 25-28 need a gonadotrophin dose 50% higher than normal weight women (22). Obese women are also more prone to pregnancy complications such as miscarriage (23), gestational diabetes, hypertension, macrosomia and difficult delivery (24).

Multiple observational studies report that weight loss is associated with improved spontaneous ovulation rates in women with PCOS (15), even after losing $<5\%$ of body weight (25). Weight loss is therefore recommended as first-line therapy in obese women with and without PCOS seeking pregnancy. This recommendation is based on extrapolation from the benefits of weight loss seen in medical conditions, such as diabetes and cardiovascular disease. There is a paucity of studies suggesting that weight loss prior to conception improves live birth rate in obese women with or without PCOS (26).

The guidelines for dietary and lifestyle intervention in PCOS have been proposed (26). Lifestyle modification is the first form of therapy, combining behavioral (reduction of psychosocial stressors), dietary, and exercise management. Reduced-energy diets (500–1000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7% to 10% over a period of 6 to 12 months. Structured exercise is an important

component of a weight-loss regime; aim for >30 minutes per/day. These interventions should be conducted prior to pregnancy and not during ovulation induction as the effects of calorie restriction and increased physical activity in the periconceptual period are unknown (27).

4.2 Medical induction of ovulation

4.2.1 Dopamine agonists

Three dopamine agonists, bromocriptine, cabergoline and quinagolide, are licensed for treatment of hyperprolactinaemia. Experience with bromocriptine is far more extensive and therefore for women undergoing ovulation induction, this drug remains the treatment of choice, with cabergoline and quinagolide as acceptable second-line drugs in patients who are intolerant of bromocriptine (28).

Mechanism of action

The secretion of prolactin from the lactotroph cells in the anterior pituitary gland is mainly regulated by the tonic inhibitory control of a prolactin inhibiting factor, which in humans is predominantly dopamine. Drugs with dopaminomimetic activity lower prolactin secretion, restore gonadal function and shrink a prolactinoma if present.

Regimen and monitoring

Bromocriptine is given at a daily dosage of 2.5 to 20 mg in divided doses 2-3 times a day. Serum prolactin concentrations are regularly measured and ovulation is checked by mid-luteal progesterone concentrations. Other forms of monitoring for ovarian response are not required as its use is not associated with multiple pregnancy or ovarian hyperstimulation syndrome (OHSS).

Cabergoline and quinagolide have longer biological half lives than bromocriptine. Cabergoline can be taken once or twice weekly and quinagolide once daily.

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.

Results

Bromocriptine can normalize serum prolactin concentrations in 80–90% of patients with

microprolactinomas and about 70% of those with macroprolactinomas, together with a decrease in tumour size (7, 9). Dopamine agonist therapy restores ovulation in about 90% of women with anovulation related to hyperprolactinaemia.

A prospective study suggested that the overall estimated rates of remission at 5 years in patients treated with bromocriptine were 76% among patients with non-tumoral hyperprolactinaemia, 67% among those with microprolactinomas, and 57% among those with macroprolactinomas (29).

Cabergoline (30-31) and quinagolide (32-33) are shown to be significantly more effective than bromocriptine in restoring normal prolactin concentrations and ovulatory cycles. Quinagolide is probably less effective than cabergoline in hyperprolactinaemic patients (28).

It is recommended that the minimal length of dopamine agonist therapy in patients with prolactinoma should be one year (7). Normalisation of MRI prior to the withdrawal of dopamine agonists and longer duration of the drug therapy are significant predictors of remission (34). If a patient has normal prolactin concentrations after dopamine agonist therapy for at least three years and the tumour volume is markedly reduced, a trial of tapering and discontinuation of these drugs may be initiated. Long term follow-up is essential with close monitoring for recurrent hyperprolactinaemia and renewed tumour growth.

Side-effects

Side-effects with bromocriptine are common and include nausea, vomiting, abdominal cramps, vertigo, postural hypotension, headaches and drowsiness. Although they are usually transient and mild, around 12% of patients discontinue the treatment for this reason (28). The side-effects can be minimised by increasing the dose gradually from a low starting dose given with a meal in the evening, or by administering vaginal bromocriptine. A slow release oral preparation may also reduce the incidence of side-effects. Significantly lesser side effects were reported in patients taking cabergoline and quinagolide when compared with bromocriptine (28).

There is no increase in the incidence of multiple pregnancy, OHSS and spontaneous abortion with dopamine agonists.

Neither bromocriptine, cabergoline nor quinagolide has been associated with any detrimental effect on pregnancy or fetal development (28). It is still recommended that patients with microprolactinomas or idiopathic hyperprolactinaemia stop bromocriptine treatment once pregnancy has been confirmed in order to avoid any potential harmful effects. Continuation of bromocriptine therapy during pregnancy may be considered in cases of macroprolactinoma or where there is evidence of tumour expansion (7, 9).

While there is considerable experience of bromocriptine use in women undergoing ovulation induction and during pregnancy, data on other dopamine agonists used in pregnancy are still limited.

The European Medicines Agency has recommended new warnings and contraindications for ergot-derived dopamine agonists as a result of the risk of fibrosis, particularly cardiac fibrosis, associated with chronic use. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine and patients should be monitored during treatment (35). Women who are planning pregnancy are further advised to stop taking cabergoline one month before they try to conceive.

4.2.2 Anti-oestrogens

4.2.2.1 CC

CC is commonly used as the first line drug in women who suffer from normogonadotrophic anovulation (WHO group II).

Mechanism of action

It is an orally active non-steroidal compound with both estrogenic and anti-estrogenic properties with its primary mechanism of action based on the anti-oestrogenic property. It displaces endogenous oestrogen from oestrogen receptors in the hypothalamic-pituitary axis, which diminishes its negative feedback and increases the secretion of GnRH and thus gonadotrophins. The increase in FSH and LH stimulate the production of ovarian follicles and subsequent ovulation.

Regimen and monitoring

CC should be started at 50 mg per day for five days following a spontaneous or

progestin-induced withdrawal bleeding. The recommended maximum dose is 150 mg per day as there was no clear evidence of efficacy at higher doses and the FDA recommended a maximum of 750 mg per treatment cycle (27). Starting from day 2, 3, 4 or 5 of the cycle was not shown to influence the results (36).

Ovulation usually occurs within 5-10 days after the last tablet. If there is no ovulation, the dose is increased at increments of 50 mg per cycle until ovulation occurs, or a maximum dose of 150 mg daily is reached.

While 50 mg per day is the recommended dose in the first cycle, a meta-analysis of 13 published reports suggests that only 46% will ovulate at this dose, a further 21% will respond to 100 mg and another 8% will ovulate with 150 mg per day (37).

Although results of large trials suggest that monitoring by ultrasound or progesterone is not mandatory to ensure good outcome (17), it is recommended to monitor the response at least during the first treatment cycle to ensure an appropriate dose is received (38). Transvaginal pelvic ultrasound should be used to monitor follicular growth and endometrial thickness. Patients who have no or excessive response to the current dose of CC and show reduced endometrial thickness can be identified. Serum progesterone concentrations could also be measured in mid-luteal phase to check for ovulation.

Duration of treatment

Treatment should generally be limited to six (ovulatory) cycles (39). A course of six ovulatory cycles is usually sufficient to know if pregnancy will be achieved. Studies had reported that 71-87.5% of pregnancies achieved with CC occur within the first three cycles of treatment (16, 40-41)

Further cycles (with a maximum of 12 in total) may be considered on an individual basis after discussion with the patient. However, second-line treatment should be considered for patients not conceiving after 6 ovulatory cycles of CC.

Further use of CC beyond 12 cycles has been found to be associated with an increased risk of ovarian cancer (RR 11.1, 95% CI 1.5-82.3) (42) and is thus not recommended.

Results

A compilation of published results from 5,268 patients revealed an ovulation rate of 73% per patient, pregnancy rate of 36% per patient and live birth rate of 29% per patient (39).

A Cochrane meta-analysis (43) of three studies (44-46) comparing CC versus placebo in patients with anovulatory subfertility showed a large and consistent benefit of CC compared to placebo (OR 5.77, 95% CI 1.55-21.48; $P < 0.009$). Analysis for ovulation rate (per woman) also showed a benefit of CC compared with placebo (OR 7.47, 95% CI 3.24-17.23; $P < 0.00001$). There is no increase in spontaneous abortion or congenital abnormalities in CC-induced pregnancies.

CC in combinations

a) CC plus tamoxifen

One small RCT (47) of 20 participants comparing CC (50 mg) plus tamoxifen (20 mg) versus CC (100 mg) alone showed no significant differences in pregnancy (OR 3.32, 95% CI 0.12-91.60) and ovulation rate (OR 14.54, 95% CI 0.67-316.69) between two groups. There were no instance of OHSS in either group and all pregnancies were singleton.

b) CC plus ketoconazole

One RCT (48) comparing CC (up to 150 mg) plus ketoconazole 400 mg with CC alone showed no evidence of difference in pregnancy rate (OR 2.37, 95% CI 0.88-6.40), multiple pregnancy rate (OR 1.18, 95% CI 0.37-3.78) and miscarriage rate (OR 0.28, 95% CI 0.01-7.081).

c) CC plus bromocriptine

One RCT (49) comparing CC (200 mg) plus bromocriptine (7.5 mg) versus CC (200 mg) showed no evidence of difference in pregnancy (OR 0.98, 95% CI 0.33-2.96) and ovulation rate (OR 1.33, 95% CI 0.47-3.79).

d) CC plus dexamethasone

Analysis of three RCTs (50-52) comparing CC (50 to 200 mg) plus dexamethasone (0.5 to 2.0 mg) with CC (50 to 200 mg) showed a large and consistent benefit of pregnancy rate in the CC plus dexamethasone group (fixed OR 9.46, 95% CI 5.05-17.7, $P < 0.00001$). When the study (50) using 0.5mg was excluded and only the two studies (51-52) using 2mg were analysed, the OR was 25.3 (95% CI 13.7-46.6, $P < 0.00001$) in favor of CC plus dexamethasone.

There was no significant difference in the incidence of multiple pregnancies per women (OR 7.71, 95% CI 0.38-155.64). No side effects were reported in either group.

e) CC plus combined oral contraceptive pills

One RCT (53) comparing CC (100 mg) plus combined oral contraceptive pills which are given for one month prior to CC Vs CC (100 mg) showed a benefit of CC plus combined pills in the pregnancy rate (OR 27.18, 95% CI 3.14- 235.02) and the NNT was 2.0 (95% CI 1.4-3.4). Ovulation rate also showed a benefit in favor of CC plus combined pills (fixed OR 26.71, 95% CI 4.91-145.38) and the NNT was 1.6 (95% CI 1.2-2.4). There was no evidence of difference in miscarriage rate (OR 1.0, 95% CI 0.06-16.97) or multiple pregnancy rate per woman (OR 7.98, 95% CI 0.39-163.33) between the two groups.

f) CC plus hCG

Analysis of two RCTs (54-55) showed no significant difference in pregnancy rate between the two groups with or without hCG (OR 1.18, 95% CI 0.59-2.36).

There was also no difference in the incidence of spontaneous abortion or miscarriage reported (OR 0.70, 95% CI 0.19-2.62). Multiple pregnancy rate was reported in one study (55) which showed no significant difference (OR 2.21, 95% CI 0.19-24.98)

g) CC plus hormone supplementation with oestradiol

One RCT (56) showed no significant difference for ovulation rate (OR 1.34, 95% CI 0.42-4.27), pregnancy rate (OR 0.42, 95% CI 0.07-2.46) or incidence of adverse events between the groups with or without hormone supplementation.

Failure of CC treatment

a) Failure to ovulate

Women who do not ovulate while receiving the 150 mg dose are considered to be CC resistant. Inability of CC to induce ovulation is more likely in patients who are obese, insulin resistant and hyperandrogenic compared with those who do respond (16).

b) Failure to conceive

Only about 50% of women who ovulate with CC will conceive. This may be partly explained by the peripheral anti-estrogenic effect of CC at the level of endometrium and

cervical mucus or by hypersecretion of LH. The two commonest causes of failure to conceive in response to CC are the presence of other subfertility factors, and the failure to persist with repeated attempts.

Side effects

Side effects of CC are related to its combined estrogenic and antiestrogenic properties, which include hot flushes, breast discomfort, abdominal distension, nausea, vomiting, nervousness, sleeplessness, headache, mood swings, dizziness, hair loss and disturbed vision. CC is usually very well tolerated with the side effects being dose dependent and usually completely reversible once CC is stopped.

Approximately 7% of pregnancies resulting from CC-induced ovulation are twin pregnancies and 0.5% are triplet pregnancies (57). While mild ovarian enlargement is relatively common, severe OHSS is very rare.

4.2.2.2 Tamoxifen

Tamoxifen is a triphenylethylene derivative with a structure similar to CC. The suggested dose in ovulation induction is 20-40 mg daily, beginning on cycle day 3 for 5 days.

A meta-analysis (58) including four RCTs (59-62) comparing tamoxifen and CC showed similar ovulation rates (OR 0.755, 95% CI 0.513–1.111). There were no significant differences in pregnancy rate per cycle (OR 1.056, 95% CI 0.583-1.912) and per ovulatory cycle (OR 1.162, 95% CI 0.632-2.134) between the two groups.

There were no instance of OHSS or multiple pregnancies and there was no difference in the incidence of miscarriage in one trial (60) reporting this outcome (OR 0.37, 95% CI 0.01-9.45).

While efficacy and safety of tamoxifen in ovulation induction has been shown, tamoxifen is not licensed for that purpose and patients should be counseled for its off-label use.

4.2.3 Insulin sensitising agents

Mechanism of action

Insulin resistance is one of the recognised metabolic disturbance associated with PCOS, and may arise from either genetic defects or obesity. Insulin-sensitising agents increase the insulin responsiveness in target tissues and hence reduce the compensatory hyperinsulinaemia, thereby ameliorating the

associated metabolic effects. They include the biguanides and thiazolidinediones.

Metformin is one of the most commonly used biguanide. It does not stimulate insulin release and hence not cause hypoglycaemia when used alone. In PCOS patients, it has been shown to improve glucose tolerance and lipid profiles, and decrease proinflammatory markers.

Regimen

500 mg tds or 850 mg bd with meals

Efficacy

A recent Cochrane review (63) assessed the effectiveness of insulin sensitising drugs in fertility treatment for women with PCOS.

(a) Metformin monotherapy

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).

Compared with CC, metformin gives 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). There are no difference in the miscarriage rate (OR 0.94; 95% CI 0.42–2.07) and the multiple pregnancy rate (OR 0.33; 95% CI 0.02–6.69) between the two treatments.

(b) Metformin co-treatment with CC

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 livebirth rate (OR 1.05; 95% CI 0.75–1.47) compared with CC alone.

Previous subgroup meta-analyses indicated a higher clinical pregnancy rate after co-treatment with metformin and CC compared with CC alone in obese patients only (OR 3.72; 95% CI 1.23–11.22) but not in non-obese patients (OR 2.71; 95% CI 0.96–7.63), and in CC-resistant subjects only (OR 9.62; 95% CI 2.95–31.45) (64).

Another systematic review (Moll et al, 2007) also indicated that metformin plus CC led to higher livebirth rates than CC alone only in CC-resistant women (RR 6.44; 95% CI 1.19–

34.90) but not in CC-naïve women (RR 1.04; 95% CI 0.82–1.33).

Side effects

Side effects include dose-dependent gastrointestinal upset including nausea, vomiting, diarrhoea. Lactic acidosis is a rare though serious complication, and hence metformin should not be prescribed to patients with renal, hepatic or major cardiovascular disease or hypoxia.

Use of other insulin sensitizing agents in PCOS patients

Examples include rosiglitazone and pioglitazone. It was showed that rosiglitazone improved ovulation rate (OR 31.0; 95% CI 3.76–255.30) but result in a higher incidence of weight gain (63). On the hand, these drugs are classified as FDA category C. There is no data on the role of pioglitazone in fertility treatment.

4.2.4 Aromatase inhibitors

Aromatase inhibitors have been used for many years as an adjunct treatment for breast cancer and are gaining in popularity as an agent for ovulation induction in patients with PCOS. Its use in combination with gonadotrophin in ovarian stimulation protocol for patients, in whom high oestradiol level would be contraindicated, for example breast cancer patients, is also advocated.

Letrozole is a third-generation aromatase inhibitor and is the most commonly used agent in ovulation induction. When compared with CC, letrozole does not have the anti-oestrogenic effects and has a much shorter half life. However, the use in ovulation induction is an off-label use.

Mechanism of action

Aromatase catalyzes the rate-limiting final step in oestrogen (E) production, the hydroxylation of androstenedione to oestrone and of testosterone to oestradiol. By blocking E production, it increases FSH secretions with a decrease in the estrogenic negative feedback of the hypothalamic-pituitary axis. Because aromatase inhibitors block high levels of E from androgen conversion, the effects in women with PCOS are more prominent.

Regimen and monitoring

The regimen is 2.5 to 5 mg per day for five days from day 3-7 of the period (65-67), or as a single dose of 20 mg on day 3 of the period

(68). A prolonged duration for 10 days has been evaluated (69).

The monitoring is similar to that of CC and usually starts on D7 of menses. Further monitoring depends on the growth of the follicles. With the split dose regimen, multiple developing follicles appear on cycle day 7, but at mid-cycle only a single dominant follicle is found.

Results

In a review (70), letrozole gave an ovulation rate of 70–84% and a pregnancy rate of 20–27% per cycle in PCOS women resistant to CC. Both of the single dose and split dose regimens achieved similar clinical pregnancy rates (68) More follicles developed and a higher clinical pregnancy rate were reported in the longer letrozole regimen (2.5 mg daily for 10 days) when compared with the standard regimen (5 mg daily for 5 days). (69)

Other aromatase inhibitors have been compared with letrozole. In a prospective study (71), 22 PCOS women were assigned to letrozole (2.5 mg per day for 5 days) and 18 to anastrozole (1 mg per day for 5 days). Letrozole was associated with a significantly higher ovulation rate (84.4% versus 60.0%) and pregnancy rate (27.0% versus 16.6%) than anastrozole.

Comparison to other methods

A meta-analysis (72) of four prospective randomized studies (67, 73-75) reveals that the overall effects of letrozole in comparison with CC was neither significant for ovulatory cycles (OR = 1.17; 95% CI 0.66–2.09), nor for pregnancy rate per cycle (OR = 1.47; 95% CI 0.73–2.96) and for pregnancy rate per patient (OR = 1.37; 95% CI 0.70–2.71).

In a Cochrane review (76) on different ovarian stimulation protocols in IUI treatment, five studies comparing CC with letrozole also found no significant difference in the pregnancy rate (OR 1.2 95% CI 0.64-2.1).

Side effects

Letrozole is well tolerated. Fatigue, nausea, constipation, diarrhea, headache, drowsiness and dizziness are common side effects.

The multiple pregnancy rate was significantly lower in letrozole, both 2.5 mg daily or 5 mg daily, comparing with CC treatment as the letrozole treatment gave

more monofollicular development comparing with CC as shown by earlier reports. However, in the recent RCT (77) on the pregnancy outcome after CC or letrozole treatment, the chance of twin pregnancies of letrozole was comparable to that of CC (8.3% vs 9.1%). There was also a case report of a triplet pregnancy resulting from ovulation induction in a PCOS woman resistant to CC treatment (78).

The teratogenic effects of letrozole are well described in animal studies (79-80). Biljan et al. (81) in an abstract 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. In a retrospective study with a much larger sample size, Tulandi et al. (82) 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.

4.2.5 Gonadotrophin-releasing hormone (GnRH)

Mechanism of action

GnRH administered in a pulsatile fashion restores the normal pattern of gonadotrophin secretion of a spontaneous menstrual cycle, leading to the development of a single dominant follicle.

Regimen and monitoring

Pulsatile GnRH is given by the subcutaneous or intravenous route through a small butterfly cannula using a small battery-operated pump which delivers 2.5–20.0 µg per bolus at 60–120 minute intervals. The intravenous route is preferred by some because more physiological LH profiles and higher ovulatory rates result when GnRH is administered intravenously (83). Higher dosage (10 µg per bolus) given at lower intervals (120 minutes) are just as effective as lower dosage (2-5 µg per bolus) given at a higher rate (every 60-90 minutes) (84).

Treatment can be monitored by regular serum oestradiol measurements and pelvic ultrasound at regular intervals. Couples are advised to have regular intercourse during the treatment cycle. The luteal phase has to be supported, either by continuing with the same regimen of pulsatile GnRH administration or using exogenous hCG injections.

Results

Hypogonadotrophic patients of normal or low weight are the best candidates for this treatment. A cumulative pregnancy rate of 80% after six cycles and up to 93% after 12 has been reported (85). It is recommended to continue this therapy for at least 12 cycles in the absence of other subfertility factors.

A Cochrane review did not find evidence to show the effectiveness of pulsatile GnRH in women with polycystic ovary syndrome (86).

Side-effects

Multiple pregnancy rates ranged between 3.8–13.5% (87-90). The risk of multiple pregnancy is predominantly present in the first cycle and is related to higher pulse dosages (87). Therefore, this risk can be greatly reduced if lower pulse dosages are employed at a lower frequency for the first cycle.

OHSS has never been described with pulsatile GnRH administration.

Patients may be reluctant to use the pulsatile GnRH therapy because of inconvenience, worry about pump failure and the problems of the needle being left in situ for a long time (e.g. displacement, local reaction, infection). As a result, it is used in very few patients for whom alternatives such as gonadotrophin treatment are available.

4.2.6 Gonadotrophin

Table 2: Different gonadotrophin preparations

Preparation	Source of FSH	FSH activity (IU / ampoule)	LH activity (IU / ampoule)	Non-FSH urinary proteins
HMG	Urine	75	75	95%
Urinary FSH	Urine	75	<0.7	95%
Urinary FSH-high purity	Urine	75	<0.001	<1%
Recombinant FSH	Chinese hamster ovary	50, 75, 100, 150, 200	None	None

HMG = human menopausal gonadotrophin;

FSH = follicle stimulating hormone

Human menopausal gonadotrophins (HMG) are extracted from urine of postmenopausal women. Besides the difficulty in collecting urine, urinary gonadotrophins contain other non-FSH urinary proteins and hence have a higher incidence of local allergic reactions and batch-to-batch inconsistency. Recombinant human FSH (rFSH)

is a pure FSH preparation, devoid of the disadvantages associated with urinary gonadotrophins and allows self subcutaneous injection, but is generally more expensive. There is no difference between urinary FSH and rFSH in ovulation and pregnancy rates, as well as in the incidence of miscarriage, ovarian hyperstimulation syndrome, multiple pregnancy and duration of stimulation (91).

Mechanism of action

The use of exogenous gonadotrophins is to overcome the FSH threshold required for the follicular development.

FSH is the key gonadotrophic hormone during the follicular phase and only minute amounts of LH are needed in different stages of follicular development and function. However, in women with hypogonadotropic hypogonadism a preparation containing both FSH and LH gives better outcome than purely FSH (92) because of the fundamental role of LH in ovarian steroidogenesis to produce an adequate serum oestradiol concentration for optimal endometrial proliferation.

Regimens

(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 (27) and the daily dose is increased by 37.5 IU at weekly intervals up to a maximum of 225 IU/day if there is no evidence of ovarian response. The same dose is maintained once follicular growth is observed. Once 1 to 2 dominant follicles reach 18 mm in mean diameter, human chorionic gonadotrophin (hCG) is administered at a dose of 5000-10000 IU to induce ovulation. The couple is advised to have intercourse on the day of hCG injection and on the following day.

As it may take several weeks to achieve an ovarian response in those with a high FSH threshold, patients should be counseled about the time scale prior to the first treatment cycle. In subsequent cycles, the patient can then be started at a dose that gives rise to ovarian response in the first cycle and this will shorten the duration required.

An original approach was the “conventional dose step-up” regime, where gonadotrophin is

commenced at 150IU/day and stepped up by increments of 75IU every 4 to 5 days till ovarian response is evident (93). Compared to the “chronic low-dose step up” approach, the duration of stimulation is shorter but the incidence of multiple pregnancy and ovarian hyperstimulation is higher, especially in patients with PCOS.

(b) Step down protocol

The aim of this protocol is to mimic the physiological changes of normal cycles. Gonadotrophin injection is commenced at 150 IU/day starting on day 2-3 of the cycle and the ovarian response is monitored by transvaginal scanning every 2-3 days. The same dose is continued until a dominant follicle ≥ 10 mm is seen on scanning, and is then reduced to 112.5 IU/day followed by a further decrease to 75 IU / day 3 days later, which is continued until hCG is administered to induce ovulation. Hence it requires more intense monitoring than the step up protocol.

According to the largest randomized trial (94), the step down regime 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 regimes.

Monitoring

Ovarian response is monitored during gonadotrophin treatment to allow for adjustment of the gonadotrophin dose, timing the hCG injection for ovulation trigger and cancellation of cycles with excessive response. Both serum oestradiol concentrations and ultrasound examination are commonly used for monitoring purposes. Serum oestradiol concentration reflects the total amount of oestradiol secreted from growing follicles but not the precise number of follicles. Ultrasound examination gives an immediate result of the number of dominant follicles and their sizes. Sholam et al., (95) has shown that oestradiol concentrations did not add any additional information to the monitoring solely based on ultrasound.

Concomitant use

(a) With gonadotrophin releasing hormone agonists (GnRH-a)

High LH concentrations commonly found in the follicular phase of patients with PCOS are associated with an increased rate of

spontaneous abortion. Premature luteinisation may occur in some patients before the dominant follicle reaches 16-18mm in mean diameter. The use of GnRH-a prior to gonadotrophin administration will lower the tonic high LH concentrations during the follicular phase and prevents the occurrence of premature LH surges. This may be used in patients with a previous history of premature luteinisation. However, a meta-analysis (96) of three randomised trials shows that there is no clear advantage in the routine use of GnRH-a in conjunction with gonadotrophin for ovulation induction in patients with CC-resistant PCOS. Common odds ratios for pregnancy per treatment cycle and moderate to severe OHSS are 1.5 (95%CI: 0.72-3.12) and 1.40 (95% CI: 0.5-3.92) respectively. Moreover, the use of GnRH-a will further increase the cost of gonadotrophin treatment because of the GnRH-a and the increased amount of gonadotrophins used after using GnRH-a.

(b) With CC

A combination of CC and gonadotrophin has been used to lessen the overall cost by reducing the amount of gonadotrophin needed. CC is used initially (100mg daily from days 2–6) for follicular recruitment, followed by gonadotrophin (150IU daily or on alternate days) to promote follicular growth, thus reducing the gonadotrophin requirement by up to 50%. This regimen is only of use in anovulatory patients who have endogenous gonadotrophins.

Results

The 6-month cumulative pregnancy rate in non-PCOS patients is around 90% with a miscarriage rate of 25% whereas the corresponding rate in PCOS is only 50-60% with a miscarriage rate of 30-40%. Conventional dose step up protocol in PCOS patients leads to 5% severe OHSS rate and 34% multiple pregnancy rate. When chronic low-dose step up protocol is used in these women, similar pregnancy rates are achieved but the rates of severe OHSS and multiple pregnancy can be reduced to <0.1% and 6% respectively.

Side-effects

Serious complications of gonadotrophin therapy include ovarian hyperstimulation syndrome and multiple pregnancy. Other complications include local reaction at the site of the injection or rarely anaphylactic reaction, perhaps due to the protein content of the urinary products. Such patients should be switched to recombinant FSH preparations.

4.3 Surgical induction of ovulation

Laparoscopic ovarian drilling (LOD) is the preferred surgical method of ovulation induction over ovarian wedge resection, which is associated with a higher risk of postsurgical adhesion formation converting hormonal subfertility to mechanical subfertility.

Mechanism of action

The mechanism of action of LOD is thought to be related to the destruction of ovarian androgen-producing tissue and the decrease of the peripheral conversion of androgens to oestrogens. A fall in the serum concentrations of androgens and LH and an increase in FSH concentrations have been demonstrated after LOD.

Regimen and monitoring

Electrocautery is commonly used in LOD. The procedure includes penetration of the ovarian capsule making four punctures per ovary and electrocautery is given at a power setting of 30 Watts applied for 5 seconds per puncture (97-98). Another commonly used method is laser vaporisation using carbon dioxide, argon or Nd:YAG crystal lasers.

Results

The ovulation rate after LOD in CC-resistant PCOS women was 52 to 67% (99). The ovulation rate in PCOS women with LOD as the first-line treatment was 64% (100). The pregnancy rate after LOD in CC-resistant PCOS women was 67% (98).

Comparison to other methods

The theoretical advantages of LOD are multiple attempts of pregnancy allowed, monofollicular development, reduced miscarriage rate with the normalized hormonal profile and assessment of the pelvic pathology and tubal status at the same setting.

LOD is usually the second-line treatment modality for PCOS women who fail to respond to CC, and so the comparison is usually with ovulation induction with gonadotrophins. In the Cochrane review (99), the livebirth rate of LOD is comparable to three cycles of gonadotrophins (OR 0.68, 95% CI 0.15-3.10) after 6 months of follow-up or six cycles of gonadotrophins at 12months follow-up (OR 1.12, 95% CI 0.60-2.08), with the pooled OR being 1.04 (95%CI 0.59 to 1.83). There was no difference in the miscarriage rate between LOD and

gonadotrophin therapy. The multiple pregnancy rate was reduced in the patients with LOD with comparison of ovarian drilling with or without medical ovulation and gonadotrophins only (OR 0.13, 95% CI 0.03-0.59). There was no OHSS reported in the randomised trials in the LOD groups. There was no difference in ovulation rate and clinical pregnancy rate after unilateral or bilateral ovarian drilling.

Based on an economic evaluation by (101), the cost of a live birth in PCOS women resistant to CC using LOD would be one third lower than using urinary or recombinant gonadotropin treatment cycle.

LOD has been compared with CC treatment as the first-line treatment in a randomized study (100). The pregnancy rate was higher in the CC group (44%) than the LOD group (27%), although the difference did not reach statistical significance (OR 2.1, 95% CI 0.7–5.8). The conclusion was that LOD was not superior to CC as a first-line method of ovulation induction in women with PCOS.

Side-effects

The main drawback of LOD is the need for general anaesthetic and surgery. Other complications such as adhesion formation and the risk of premature ovarian failure are of concern. The reported incidence of adhesion formation after LOD varied considerably in different studies from 0 to 100% (102-104). Most of the studies reported mild to moderate adhesions in about 35% of cases, which did not seem to affect the pregnancy rate after LOD (103).

5 RISKS OF OVULATION INDUCTION

5.1 Multiple pregnancies

In the last two decades, significant increase in the incidence of multiple births is almost entirely the result of the use of gonadotrophins and other agents for ovulation induction or assisted conception.

Spontaneous multiple pregnancies occurs in about 1-2% of women, which is increased to 7-10% of women taking CC and further increased to up to ~25% in women with CC-resistant PCOS treated with gonadotrophins (105).

Multiple pregnancies carry extra risks for both the mothers and fetuses. Obstetrics complications include increased incidence of pre-eclampsia and eclampsia, antepartum haemorrhage,

preterm labour and surgical or assisted delivery. The high incidence of prematurity and low birth weight in high order multiple pregnancies result in a 4-fold rise of perinatal mortality for twins and 6-fold rise in triplets compared with singleton pregnancies. Multiple gestation children may suffer long-term consequences of perinatal complications, including cerebral palsy and learning disabilities, as well as slow language development and behavioural problems.

In order to reduce the incidence of iatrogenic multiple pregnancies and its subsequent risks, ovulation induction should aim to restore the feedback system which selects a single follicle for ovulation.

Hyperprolactinaemic women should be treated with dopamine agonists and women with hypogonadotrophic hypothalamic amenorrhoea should be treated with pulsatile GnRH if possible, which is associated with a high incidence of single ovulation.

For women with normogonadotrophic anovulation, including PCOS, the first line treatment is CC and the ovarian response should be monitored by pelvic ultrasound especially in the first cycle or after the dose of CC has been stepped up. Incidence of twins is increased to 7-10% and that of triplets is 0.5-1% (57).

Treatment with gonadotrophins should be confined to those who are resistant to CC because multiple pregnancy is considerable (~25-36%) with the conventional 'step up' regimens (105). Low dose 'step up' or 'step down' regimens should be encouraged since they aim to maintain the physiological principle of follicle selection resulting in a high incidence of monovulation, though at the price of slightly lower pregnancy rates (106).

Patients at risk of multiple follicular development, e.g. patients with PCOS, should be identified. A lower starting dose of gonadotrophin should be used. Ovarian response should be carefully monitored with ultrasound examinations in terms of the size and number of developing follicles. Cycles with more than 2 dominant follicles should be cancelled and the starting dose should be reduced in subsequent cycles. Alternatively, the ovulation induction cycles could be converted to IVF treatment with replacement of at most two embryos only. Supernumerary follicles could be aspirated and selective fetal

reduction could be considered to help in reduction of multiple pregnancies. However, selective fetal reduction is not without complications and it should never be considered a substitute for careful monitoring.

5.2 Ovarian Cancer

Epithelial ovarian cancer is the most life-threatening gynaecological cancer with a low 5-year survival rate estimated at 30-35% when all stages are taken together (107). Epidemiological studies have linked epithelial ovarian cancer with both nulliparity and subfertility.

Increasing concerns have been raised regarding the risk of ovarian malignancy during or after ovarian stimulation. A cohort study (42) indicated a RR of 11.1 (95% CI 1.5-82) with long term use of CC (12 months or more). A collaborative analysis of 12 US case-control studies (108) 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 with women who were not subfertile.

Two hypotheses have postulated ovulation as potential biological promoters of ovarian cancer and thus increased risks of ovarian cancer with fertility drugs used in ovulation induction or stimulation. The most widely accepted hypothesis suggests that epithelial ovarian carcinoma results from repeated ovulations, where the cumulative effects of each minor trauma to the ovarian epithelium can lead to malignant transformation (Fathalla's incessant ovulation hypothesis). The second hypothesis suggests that persistent exposure of the ovary to endogenous and exogenous gonadotropins in conjunction with secondarily elevated oestradiol concentration may be directly carcinogenic (109).

A meta-analysis (110) including 7 case-control studies and 3 cohort studies showed reassuring results. The pooled data showed a significantly elevated risk of ovarian cancer in subjects exposed to fertility medications when compared with general population controls (OR 1.52; 95% CI 1.18-1.97), such an increased risk was not observed when compared with subfertile controls not exposed to fertility medications (OR 0.99; 95% CI 0.67-1.45). Indeed, cohort data comparing outcome in treated infertile patients with untreated subfertile patients suggests that treated patients may tend to a lower incidence of ovarian cancer (OR 0.67; 95% CI 0.32-1.41). It suggested that subfertility itself rather than the use of fertility drugs is the risk factor for developing ovarian cancer.

Successful fertility treatment which ended in pregnancy may actually reduce the cancer risk.

Similar reassuring findings were also obtained from a recent large cohort study (111). In 54,362 Danish women attending subfertility clinic during 1963-1998, 156 women with invasive epithelial ovarian cancer were identified during a follow up period of up to 42.6 years (median 16.0 years). The risk of ovarian cancer was 46% higher than that of the general Danish population after adjustment for parity. However, the overall risk of ovarian cancer was not significantly affected by the use of any fertility drug (RR 1.03; 95% CI 0.73-1.47), CC (RR 1.14, 95% CI 0.79-1.64), gonadotrophins (RR 0.93; 95% CI 0.50-1.37) or GnRH (RR 0.80; 95% CI 0.42-1.51) or in combinations. Risk did not differ according to the number of cycles of use, length of follow-up since first use of drug or parity. Potential confounders including various causes of infertility and any use of oral contraceptives had not been shown to affect the risk estimates.

In three studies (112-114) that have specifically examined the effect of fertility drug use on the risk of borderline tumors, a stronger association was observed than with the risk of invasive tumors. The plausibility of these results is heightened by the finding that oestrogen receptor (ER) expression is a common feature of ovarian borderline tumors (113). And it may also suggest that the increased prevalence of borderline tumors compared to invasive cancer in a younger group of women. It should however be emphasized that the association between borderline tumors and ovulation inducing drugs was not a consistent finding among different studies.

The relationship between subfertility treatment and the risk of non-epithelial ovarian malignancies is even less clear with limited data showing conflicting results (115-116).

In summary, findings to date on ovarian cancer risk associated with fertility drug treatment are reassuring, but not definitive. A stronger association has been observed between fertility drug use and borderline tumors of ovary though still not consistent.

6 RECOMMENDATION

The levels of evidence and grading of recommendation are given according to the RCOG scheme (117).

Weight loss	Weight loss is recommended as first line therapy in obese women with and without PCOS seeking pregnancy. <Evidence 4; Grade D>
Dopamine agonists	<p>Dopamine agonists are an effective treatment for anovulation related to hyperprolactinaemia. <Evidence 1++, Grade A></p> <p>Bromocriptine remains the treatment of choice for women undergoing ovulation induction because of extensive experience with this drug while cabergoline and quinagolide are acceptable second-line drugs in patients who are intolerant of bromocriptine. <Evidence 4, Grade D></p>
Clomiphene citrate (CC)	<p>CC increases ovulation and pregnancy rates with no increase in spontaneous abortion or congenital abnormalities. It should be used as the first line treatment in women with normogonadotrophic anovulation. <Evidence 1++, Grade A></p> <p>CC should be started at 50 mg daily for 5 days, at increments of 50 mg per cycle until ovulation occurs with a maximum dose of 150 mg daily. It should be continued for 6 cycles at ovulatory dose or until pregnancy occurs. <Evidence 4, Grade D></p> <p>Ovarian response should be monitored at least during the first cycle using pelvic ultrasound. <Evidence 4, Grade D></p> <p>There is no significant difference in pregnancy rate or ovulation rate between CC and tamoxifen. <Evidence 1++, Grade A></p> <p>CC in combination with dexamethasone (0.5-2.0 mg) and combined oral contraceptive pills improves pregnancy rate. <Evidence 1+, Grade A></p>
Metformin	<p>The routine use of metformin either alone or in combination with CC in fertility treatment appears to have limited efficacy. <Evidence 1++, Grade A></p> <p>In a subgroup of PCOS patients who are obese or CC-resistant, co-treatment with metformin and CC can be a second-line option before gonadotrophin induction or ovarian drilling is considered. <Evidence 1++, Grade A></p>
Letrozole	<p>Letrozole is as effective as CC in ovulation induction. <Evidence 1++, Grade A></p> <p>The use of letrozole in ovulation induction should be with caution in view of the possible teratogenic effects. <Evidence 2-, Grade D></p>
Pulsatile GnRH	Pulsatile GnRH therapy is indicated in patients with hypogonadotrophic anovulation but its use may be limited by the inconvenience of the pump. <Evidence 3, Grade D>
Gonadotrophin	<p>Women with normogonadotrophic anovulation with anti-oestrogen resistance or failure can be offered ovulation induction with gonadotrophin. <Evidence 3, Grade D></p> <p>Human menopausal gonadotrophin, urinary FSH or recombinant FSH are all equally effective and do not differ in ovulation and pregnancy rates and risk of complications. <Evidence 1++, Grade A></p> <p>For women with hypogonadotrophic hypogonadism, a preparation containing both FSH and LH should be used for ovulation induction. <Evidence 1++, Grade A></p> <p>The chronic low-dose step up regime is the recommended approach, especially for women with PCOS. <Evidence 1+, Grade A></p> <p>Ultrasound scan should be the preferred modality of monitoring for ovulation induction with gonadotrophin. <Evidence 3, Grade D></p> <p>The use of gonadotrophin releasing hormone agonist for pituitary down-regulation should not be a routine but may be considered in patients with previous history of premature luteinisation. <Evidence 1++, Grade A></p>
Laparoscopic ovarian drilling (LOD)	<p>LOD has a comparable outcome in terms of ovulation rate and pregnancy rate when compared with gonadotrophins, with a lower multiple pregnancy rate, as a second line treatment for CC-resistant PCOS women. <Evidence 1++, Grade A></p> <p>LOD was not superior to CC as a first line method of ovulation induction in PCOS women. <Evidence 1++, Grade A></p>

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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.