



HKCOG Guidelines— Induction of Ovulation

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PURPOSE AND SCOPE

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

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.

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 Organization (WHO) classification² is also given for reference (Figure 1).

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

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***Specific*

- Hyperprolactinaemia
- Kallmann's syndrome (WHO group I)

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

WHO = World Health Organization.

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 gonadotrophin-releasing hormone (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

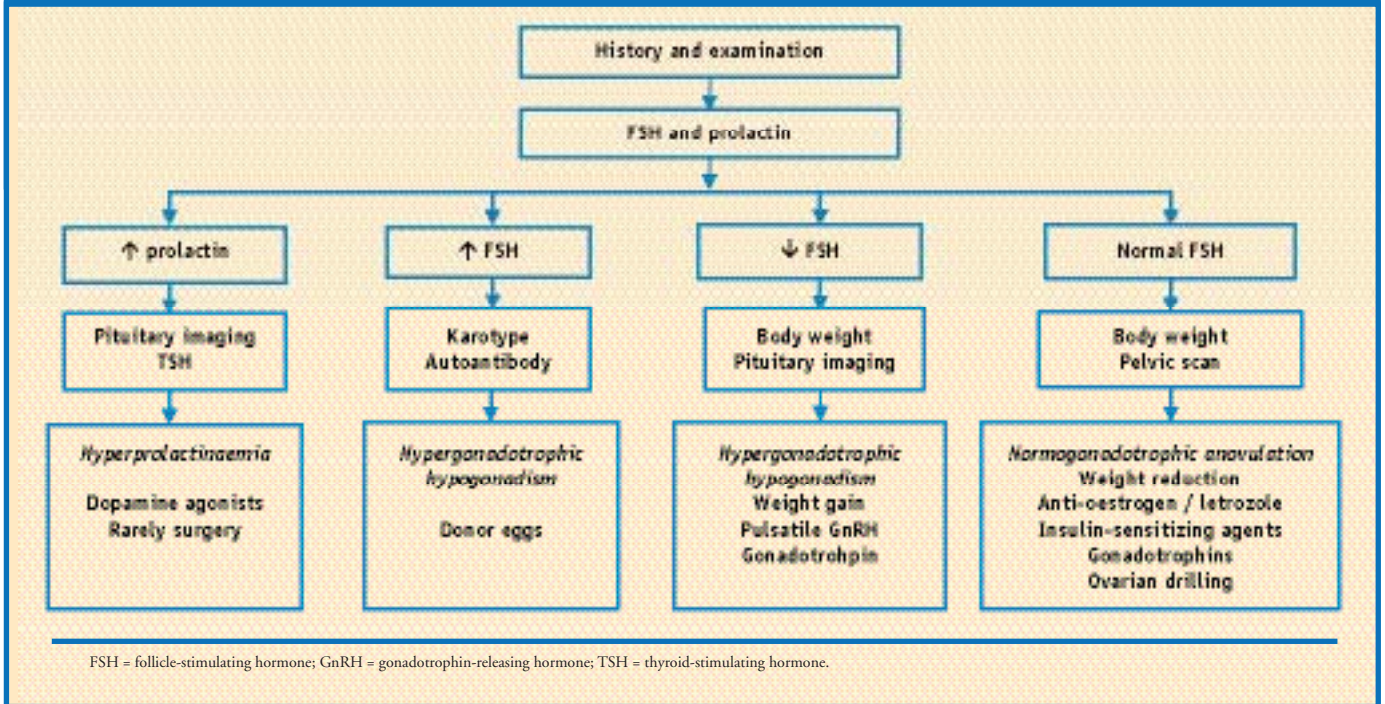
The first-line treatment is the use of dopamine agonists, which lower prolactin concentration and cause shrinkage of a prolactinoma if present. Surgery in the form of trans-sphenoidal pituitary adenectomy is seldom indicated in the presence of a prolactinoma because of high recurrence rate and possibility of panhypopituitarism.^{8,9} Radiotherapy is used very infrequently and is considered only if both medical and surgical treatments fail or are contraindicated.

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 amenorrhoea with low endogenous oestrogen and highly elevated follicle-stimulating hormone (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 spontane

Figure 1: Flowchart of diagnosis and treatment



ous 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* fertilization setting. In addition, they should be offered long-term hormone replacement therapy to protect their bones from the deleterious effects of hypoestrogenism.

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 luteinizing hormone (LH) secretion from the pituitary gland (hypog-

onadotrophic 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 LH¹³ are offered to patients with other hypogonadotrophic causes or with persisting anovulation despite weight gain.

Normogonadotrophic Anovulation (WHO Group II)

This includes a heterogeneous group of patients who can present either with regular cycles, oligomenorrhoea, or even amenorrhoea. The mid-

Patients seeking treatment for ovulation disorders should be fully informed of the treatment options available, the success of each treatment option, and the associated risks.



luteal serum progesterone is low, FSH levels are in the normal range, and prolactin is normal. Most of these patients are likely to have polycystic ovary syndrome (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 sulfate and 17-hydroxyprogesterone.

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-sensitizing 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.

TREATMENT

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

Weight Reduction

Body mass index (BMI) is more representative of body fat and is calculated as weight in kilograms divided by height in metres squared. Overweight is defined as $BMI \geq 25 \text{ kg/m}^2$ and obesity is $BMI \geq 30 \text{ kg/m}^2$.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 rates¹⁶ and lower cumulative live birth rates for women with a $BMI > 30 \text{ kg/m}^2$.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 owing 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 behavioural (reduction of psychosocial stressors), dietary, and exercise management. Reduced-energy diets (500–1,000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7–10% over a period of 6–12 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

Medical Induction of Ovulation

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 2.5–20 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.

Experience with bromocriptine is far more extensive, and therefore for women undergoing ovulation induction this drug remains the treatment of choice

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-tumoural 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 1 year.⁷ Normalization of magnetic resonance imaging 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 3 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 minimized 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.

Bromocriptine, cabergoline or quinagolide has not 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 1 month before they try to conceive.

Anti-oestrogens

Clomiphene citrate

Clomiphene citrate 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 oestrogenic and anti-oestrogenic 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 5 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 US Food and Drug Administration (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

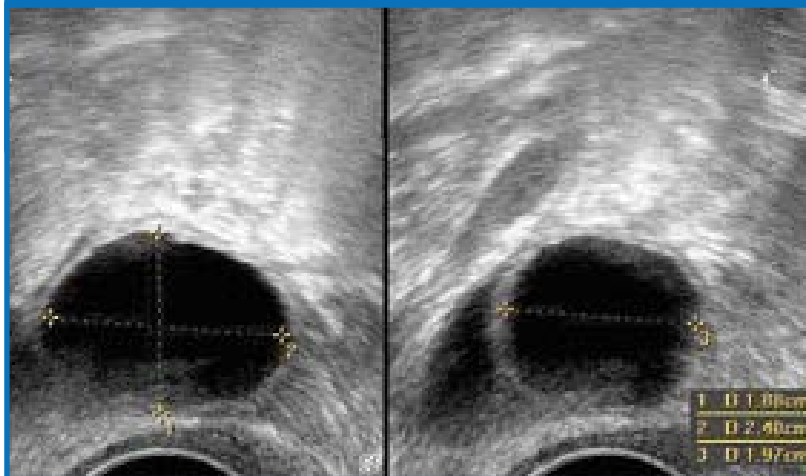
Ovulation usually occurs within 5–10 days after the last tablet. If there is no ovulation, the dose is increased at increments of 50 mg per cycle until ovulation occurs, or a maximum dose of 150 mg daily is reached.

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 that 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

The goal of ovulation induction is to achieve development of a single follicle and subsequent ovulation in women with anovulation.



to know if pregnancy will be achieved. Studies have reported that 71–87.5% of pregnancies achieved with CC occur within the first three cycles of treatment.^{16,40,41}

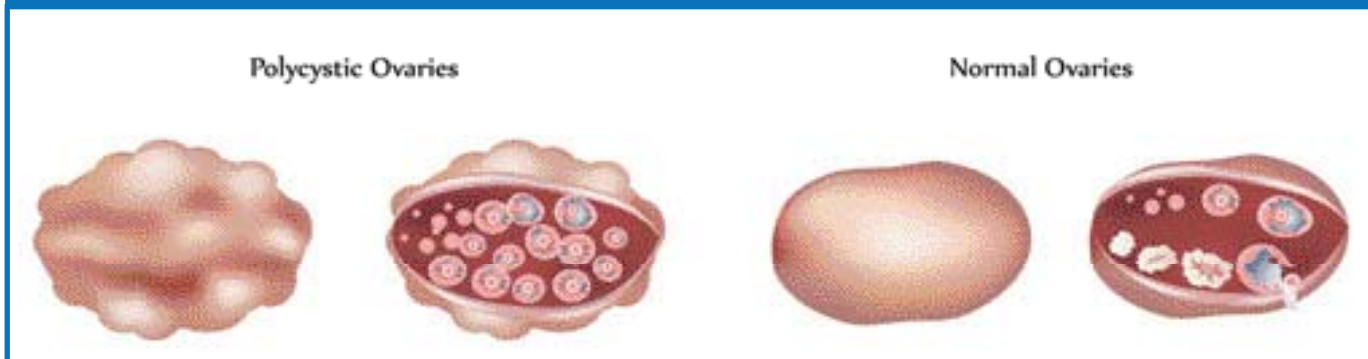
Further cycles (with a maximum of 12 in total) may be considered on an individual basis after discussion with the patient. However, second-line treatment should be considered for patients not conceiving after six ovulatory cycles of CC.

Further use of CC beyond 12 cycles has been found to be associated with an increased risk of ovarian cancer (relative risk [RR], 11.1; 95% confidence interval [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-analysis⁴³ of three studies^{44–46} comparing CC versus placebo in patients with anovulatory subfertility showed a large and consistent benefit of CC compared with placebo (odds ratio [OR], 5.77; 95% CI, 1.55–21.48; $P < 0.009$). Analysis for ovulation rate (per woman) also

Most patients with normogonadotrophic anovulation are likely to have polycystic ovary syndrome.



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. One small randomized controlled trial (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 the two groups. There were no instance of OHSS in either group, and all pregnancies were singleton.

One RCT⁴⁸ 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, 0.01–7.08).

One RCT⁴⁹ 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).

Analysis of three RCTs^{50–52} comparing CC (50–200 mg) plus dexamethasone (0.5–2.0 mg) with CC (50–200 mg) showed a large and consistent benefit of pregnancy rate in the CC plus dexametha-

none group (fixed OR, 9.46; 95% CI, 5.05–17.7; $P < 0.00001$). When the study⁵⁰ using 0.5 mg was excluded and only the two studies^{51,52} using 2 mg were analysed, the OR was 25.3 (95% CI, 13.7–46.6; $P < 0.00001$) in favour 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.

One RCT⁵³ comparing CC (100 mg) plus combined oral contraceptive pills which are given for 1 month prior to CC versus 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 number needed to treat (NNT) was 2.0 (95% CI, 1.4–3.4). Ovulation rate also showed a benefit in favour 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.

Analysis of two RCTs^{54,55} showed no significant difference in pregnancy rate between the two groups with or without human chorionic gonadotrophin (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)

One RCT⁵⁶ 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. 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

Only about 50% of women who ovulate with CC will conceive. This may be partly explained by the peripheral anti-oestrogenic effect of CC at the level of endometrium and cervical mucus or by hypersecretion of LH. The two most common 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 oestrogenic and anti-oestrogenic 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.

Tamoxifen

Tamoxifen is a triphenylethylene derivative with a structure similar to CC. The suggested dose in ovu-

lation induction is 20–40 mg daily, beginning on cycle day 3 for 5 days.

A meta-analysis⁵⁸ 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 instances of OHSS or multiple pregnancies, and there was no difference in the incidence of miscarriage in one trial⁶⁰ 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 counselled for its off-label use.

Insulin-sensitizing Agents

Mechanism of action. Insulin resistance is one of the recognized metabolic disturbance associated with PCOS, and may arise from either genetic defects or obesity. Insulin-sensitizing 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 does 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. Five hundred milligrams thrice daily or 850 mg twice daily with meals.

Efficacy. A recent Cochrane review⁶³ assessed the effectiveness of insulin-sensitizing drugs in fertility treatment for women with PCOS.

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 live birth 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 live birth 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.

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 live birth 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 review⁶⁵ also indicated that metformin plus CC led to higher live birth 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, and 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 shown 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 other hand, these drugs are classified as FDA category C. There are no data on the role of pioglitazone in fertility treatment.

Insulin resistance is one of the recognized metabolic disturbance associated with PCOS

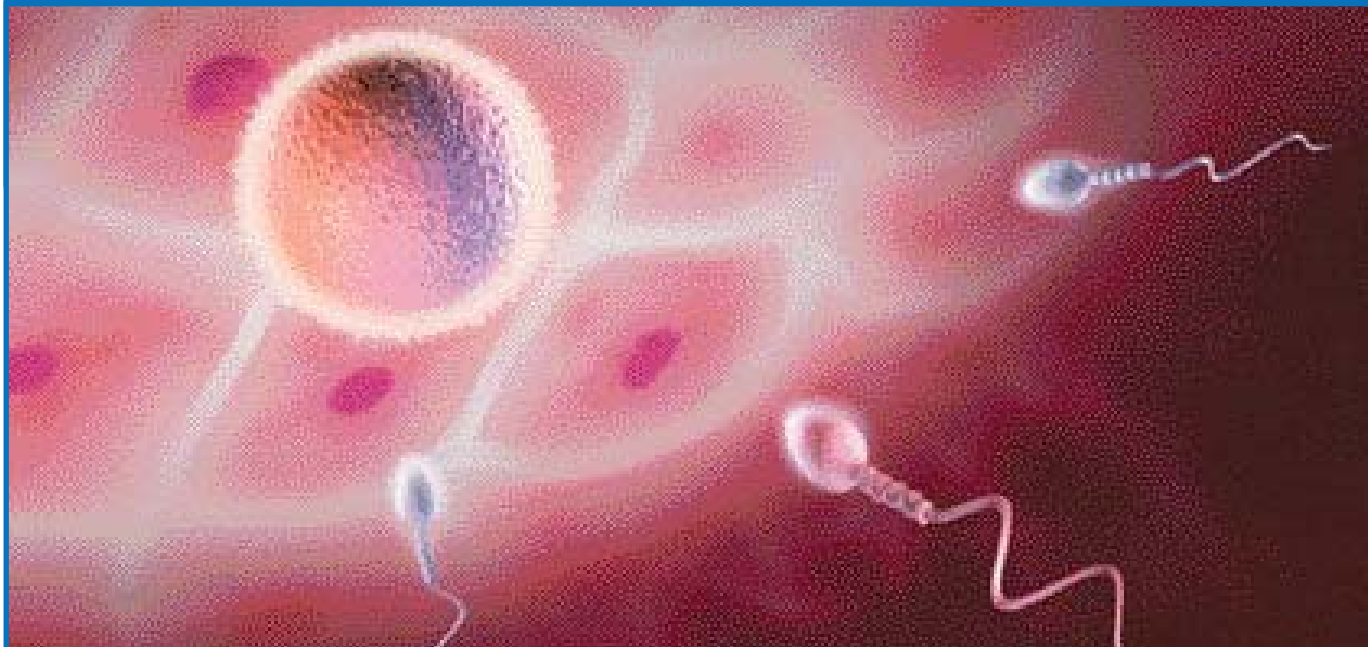
Aromatase Inhibitors

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 catalyses the rate-limiting final step in oestrogen production, the hydroxylation of androstenedione to oestrone and of testosterone to oestradiol. By blocking

Ovulation disorders account for 20% of the causes of subfertility.



oestrogen production, it increases FSH secretions with a decrease in the oestrogenic negative feedback of the hypothalamic-pituitary axis. Because aromatase inhibitors block high levels of oestrogen 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 5 days from days 3–7 of the period^{66–68}, or as a single dose of 20 mg on day 3 of the period.⁶⁹ A prolonged duration for 10 days has been evaluated.⁷⁰

The monitoring is similar to that of CC and usually starts on day 7 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,⁷¹ 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.⁶⁹ 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).⁷⁰

Other aromatase inhibitors have been compared with letrozole. In a prospective study,⁷² 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% vs 60.0%) and pregnancy rate (27.0% vs 16.6%) than anastrozole.

Comparison with other methods. A meta-analysis⁷³ of four prospective, randomized studies^{68,74–76} revealed that the overall effects of letrozole in comparison with CC was not significant for ovulatory cycles (OR, 1.17; 95% CI, 0.66–2.09), pregnancy rate per cycle (OR, 1.47; 95% CI, 0.73–2.96) and pregnancy rate per patient (OR, 1.37; 95% CI, 0.70–2.71).

In a Cochrane review⁷⁷ on different ovarian stimulation protocols in intrauterine insemination 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, diarrhoea, 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, compared with CC treatment, as the letrozole treatment gave more monofollicular development compared with CC as shown by earlier reports. However, in the recent RCT⁷⁸ 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.⁷⁹

The teratogenic effects of letrozole are well described in animal studies.^{80,81} Biljan *et al*⁸² 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*⁸³ 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.

Gonadotrophin-releasing Hormone

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 bat-

tery-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.⁸⁴ 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).⁸⁵

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.⁸⁶ 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 any evidence to show the effectiveness of pulsatile GnRH in women with PCOS.⁸⁷

Side-effects. Multiple pregnancy rates ranged between 3.8–13.5%.^{88–91} The risk of multiple pregnancy is predominantly present in the first cycle and is related to higher pulse dosages.⁸⁸ 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 (eg, displacement, local reaction, infection). As a result, it is used in

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

FSH = follicle-stimulating hormone; HMG = human menopausal gonadotrophin.

very few patients for whom alternatives such as gonadotrophin treatment are available.

Gonadotrophin (Table 2)

Human menopausal gonadotrophins are extracted from urine of postmenopausal women. Besides the difficulty in collecting urine, urinary gonadotrophins contain other non-FSH urinary proteins and hence the higher incidence of local allergic reactions and batch-to-batch inconsistency. Recombinant human FSH 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 recombinant human FSH in ovulation and pregnancy rates, as well as in the incidence of miscarriage, OHSS, multiple pregnancy and duration of stimulation.⁹²

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 FSH⁹³ 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 days²⁷ 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 one to two dominant follicles reach 18 mm in mean diameter, hCG is administered at a dose of 5,000–10,000 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 counselled 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 150 IU/day and stepped up by increments of 75 IU every 4 to 5 days till ovarian response is evident.⁹⁴ Compared with 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,⁹⁵ the step-down regime has a shorter duration of stimulation compared with the step-up protocol but a higher rate of multifollicular development and OHSS, 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*⁹⁶ has shown that oestradiol concentrations did not

add any additional information to the monitoring solely based on ultrasound.

Concomitant use. (a) With GnRH agonists.

High LH concentrations commonly found in the follicular phase of patients with PCOS are associated with an increased rate of spontaneous abortion. Premature luteinization may occur in some patients

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before the dominant follicle reaches 16–18 mm in mean diameter. The use of GnRH agonists (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 luteinization. However, a meta-analysis⁹⁷ of three randomized 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 treat

ment 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 (100 mg daily from days 2–6) for follicular recruitment, followed by gonadotrophin (150 IU 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 OHSS 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.

Surgical Induction of Ovulation

Laparoscopic ovarian drilling 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.

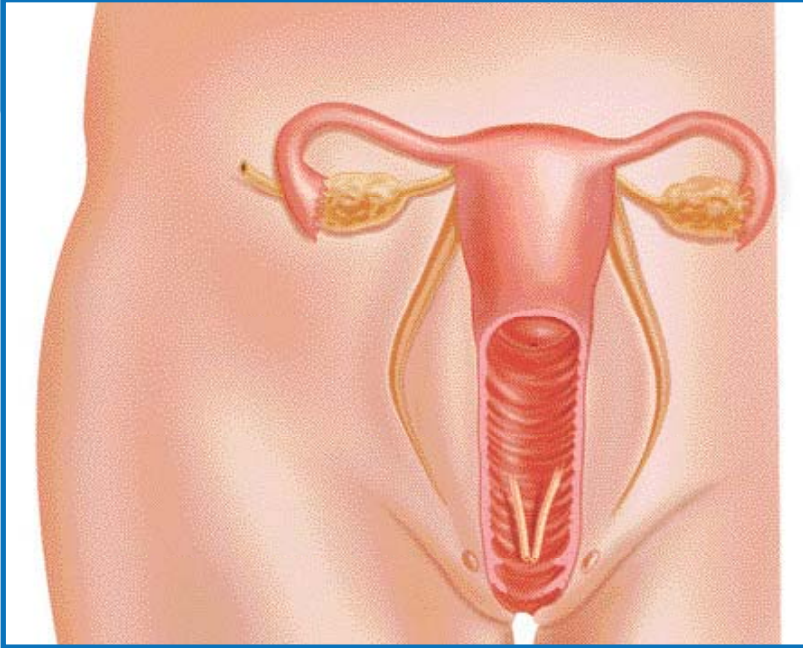
Regimen and monitoring. Electrocautery is commonly used in LOD. The procedure includes penetration of the ovarian capsule, making four punctures per ovary, and electrocautery is given at a power setting of 30 W applied for 5 seconds per puncture.^{98,99} Another commonly used method is laser vaporization using carbon dioxide, argon or Nd:YAG crystal lasers.

Results. The ovulation rate after LOD in CC-resistant PCOS women was 52% to 67%.¹⁰⁰ The ovulation rate in PCOS women with LOD as the first-line treatment was 64%.¹⁰¹ The pregnancy rate after LOD in CC-resistant PCOS women was 67%.⁹⁹

Comparison with 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 a Cochrane review,¹⁰⁰ the live birth 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 12 months' follow-up (OR, 1.12; 95% CI, 0.60–2.08), with the pooled OR being 1.04 (95% CI, 0.59–1.83). 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 com

The incidence of spontaneous multiple pregnancies is increased in women taking clomiphene citrate and further increased in those with clomiphene citrate-resistant polycystic ovary syndrome treated with gonadotrophins.



parison 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 randomized 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 Farquhar *et al*,¹⁰² the cost of a live birth in PCOS women resistant to CC using LOD would be one-third lower than using urinary or recombinant gonadotrophin treatment cycle.

LOD has been compared with CC treatment as the first-line treatment in a randomized study.¹⁰¹ 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%.^{103–105} 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.¹⁰⁴

RISKS OF OVULATION INDUCTION

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 occur 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.¹⁰⁶

Multiple pregnancies carry extra risks for both the mothers and fetuses. Obstetric 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 fourfold rise of perinatal mortality for twins and sixfold 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, ovu-

lation 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.¹⁰⁶ 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.¹⁰⁷

Patients at risk of multiple follicular development, eg, 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 two dominant follicles should be cancelled and the starting dose should be reduced in subsequent cycles. Alternatively, the ovulation induction cycles could be converted to *in vitro* fertilization 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 con-

sidered a substitute for careful monitoring.

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.¹⁰⁸ 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 study⁴² 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 studies¹⁰⁹ 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 gonadotrophins in conjunction with secondarily elevated oestradiol concentration may be directly carcinogenic.¹¹⁰

A meta-analysis¹¹¹ including seven case-control studies and three 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 ob-

Levels of evidence and grading of recommendations

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	Dopamine agonists are an effective treatment for anovulation related to hyperprolactinaemia.	Evidence 1++, Grade A
	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
CC	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
	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 six cycles at ovulatory dose or until pregnancy occurs.	Evidence 4, Grade D
	Ovarian response should be monitored at least during the first cycle using pelvic ultrasound.	Evidence 4, Grade D
	There is no significant difference in pregnancy rate or ovulation rate between CC and tamoxifen.	Evidence 1++, Grade A
	CC in combination with dexamethasone (0.5–2.0 mg) and combined oral contraceptive pills improves pregnancy rate.	Evidence 1+, Grade A
Metformin	The routine use of metformin either alone or in combination with CC in fertility treatment appears to have limited efficacy.	Evidence 1++, Grade A
	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
Letrozole	Letrozole is as effective as CC in ovulation induction.	Evidence 1++, Grade A
	The use of letrozole in ovulation induction should be with caution in view of the possible teratogenic effects.	Evidence 2–, Grade D
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	Women with normogonadotrophic anovulation with anti-oestrogen resistance or failure can be offered ovulation induction with gonadotrophin.	Evidence 3, Grade D
	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
	For women with hypogonadotrophic hypogonadism, a preparation containing both FSH and LH should be used for ovulation induction.	Evidence 1++, Grade A
	The chronic low-dose step-up regime is the recommended approach, especially for women with PCOS.	Evidence 1+, Grade A
	Ultrasound scan should be the preferred modality of monitoring for ovulation induction with gonadotrophin.	Evidence 3, Grade D
	The use of GnRH agonist for pituitary downregulation should not be a routine but may be considered in patients with previous history of premature luteinization.	Evidence 1++, Grade A
LOD	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
	LOD was not superior to CC as a first-line method of ovulation induction in PCOS women.	Evidence 1++, Grade A

CC = clomiphene citrate; FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinizing hormone; LOD = laparoscopic ovarian drilling; PCOS = polycystic ovary syndrome.

served 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 suggest 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 results in pregnancy, may actually reduce the cancer risk.

Similar reassuring findings were also obtained from a recent large cohort study.¹¹² 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 and 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^{113–115} that have specifically examined the effect of fertility drug use on the risk of borderline tumours, a stronger association was observed than with the risk of invasive tumours. The plausibility of these results is heightened by the finding that oestrogen receptor expression is a common feature of ovarian borderline tumours.¹¹⁴ And it may also suggest that the increased prevalence of borderline tumours compared to invasive cancer in a younger group of women. It should, however, be

emphasized that the association between borderline tumours 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.^{116,117}

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 tumours of ovary, though still not consistent.

RECOMMENDATIONS

The levels of evidence and grading of recommendations are given according to the Royal College of Obstetricians and Gynaecologists scheme (see the box on page 22).¹¹⁸

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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.

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