Induction of ovulation

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Abstract

Anovulatory infertility is one of the commonest causes of infertility and can be caused by problems related to the ovary (normogonadotropic and hypergonadotropic hypogonadism) or the pituitary and hypothalamus (hypogonadotropic hypogonadism). Consequently induction of ovulation will depend on the cause of infertility. For those with normogonadotropic hypogonadism, ovulation can be induced using antioestrogens such as clomifene citrate and tamoxifen or aromatase inhibitors such as letrozole. Second line treatments include metformin, gonadotropins and laparoscopic ovarian drilling. Those with hypogonadotropic hypogonadism will require gonadotropins or GnRH analogues. The following review outlines the different approaches to ovulation induction with a focus on commonly encountered clinical scenarios.

Keywords anovulation; clomid; laparoscopic ovarian diathermy; obesity; ovulation induction; PCOS

Introduction

Anovulatory infertility is one of the most commonly encountered problems in the infertility clinic. Anovulation may be due to problems affecting the ovary, pituitary or hypothalamus. Causes of anovulation have been classified by the World Health Organisation into three categories based on gonadotropin profile – follicle stimulating hormone (FSH), luteinizing hormone (LH) and also oestradiol (E2). WHO type 1 anovulation (10%) is characterized by a hypogonadotropic hypo-oestrogenic state and includes hypothalamic amenorrhoea, hypogonadotropic hypogonadism and hypopituitarism. These can be caused by any lesion affecting the pituitary or hypothalamus and affecting gonadotropin production including idiopathic, weight-related amenorrhoea, Sheehan syndrome, extreme stress and strenuous exercise, Kallman's syndrome, craniopharyngiomas etc. WHO type 2 (normogonadotropic hypogonadism) is by far the commonest cause of anovulation accounting for 85% of cases and is most commonly caused by polycystic ovarian syndrome (PCOS). Hyperprolactinaemic amenorrhoea is another, though much less common, WHO Group II ovulation disorder. Clinically, in addition to amenorrhoea and infertility, women with the condition may have galactorrhoea. The most common source of the excess prolactin production is a pituitary microadenoma. Treatment is with dopamine agonists and addressing the underlying cause. WHO type 3 anovulation (5%) (hypergonadotropic hypogonadism) is usually an indication of ovarian failure.

Induction of ovulation is possible in the first two types of anovulation. In the third type, ovulation induction is usually unsuccessful due to follicular depletion and the only way to achieve a pregnancy is through oocyte donation. The following scenarios will explore the management of different causes of anovulation more closely.

Case 1

A 28-year-old woman with anovulatory infertility due to polycystic ovarian syndrome (PCOS) and a body mass index (BMI) of 40 kg/m^2 has attended the infertility clinic to discuss options for management of her infertility. Her partner has a normal semen analysis and her hysterosalpingogram has demonstrated bilateral patent tubes. She would like to discuss her options.

Discussion

Induction of ovulation for women with PCOS is the commonest scenario for ovulation induction encountered in most infertility clinics. Choice of treatment for this patient will depend on her BMI. Weight loss is the first line of treatment in overweight and obese PCOS women while Clomiphene citrate and Aromatase inhibitors are recommended as the first line in lean PCOS ones.

Weight loss: obesity is commonly associated with PCOS and can have a detrimental effect on reproductive performance. The central fat compartment is a metabolically active unit that produces a number of substances known as adipokines that can adversely affect reproductive function. Obesity is associated with resistance to ovulation induction using antioestrogens as first line treatment, increases the gonadotropin doses required in second line treatments and pose a higher technical risks if laparoscopy is needed down the line. Weight loss would both improve fertility as well as decrease the risks that obesity may pose to an ensuing pregnancy. Even a small decrease in the BMI may be accompanied by a dramatic improvement in reproductive performance. Strategies for weight loss include:

- Lifestyle interventions:

Multi-component interventions are the treatment of choice and effective weight management programmes should include behavioural changes to increase the person's physical activity levels or decrease inactivity. Behavioural changes include goal setting, stimulus control, relapse prevention etc. Improved eating behaviour and the quality of the person's diet are important as is reduction in energy intake. However, unduly restrictive and nutritionally unbalanced diets are ineffective in the long term and can be harmful.

- Anti-obesity drugs:

Consideration should be given to pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated. Pharmacological agents are mainly indicated when patients fail to lose significant weight despite lifestyle changes and a low calorie diet or may be used to maintain weight loss rather than for continued weight loss. There are two main classes of drugs classified according to the site of

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action; namely centrally and peripherally acting drugs. The only available representative of the peripherally acting group is intestinal and pancreatic lipase inhibitor Orlistat, which acts by decreasing fat absorption from the intestinal lumen by about 30%. Sibutramine, a centrally acting anti-obesity agent should not be used as it has been withdrawn from the UK market after a report from the European Medicines Agency that the cardiovascular risks associated with its use outweighed the benefits.

Furthermore, when choosing the appropriate weight-losing drug, it is paramount to consider the safety of these drugs should a woman conceive whilst receiving them. In this regard, Orlistat's pharmacokinetics places it in a favourable position due to its low absorption and first-pass metabolism resulting in a bioavailability of less than 1%.

Finally and regarding the efficacy of Orlistat in restoring ovulation, current evidence suggests that Orlistat can lead to similar ovulation rates to metformin when used over a three-month period.

- Bariatric surgery:

As a final option, bariatric surgery can be used for those who have failed to lose weight by other means. The guidelines of the National Institute for Health and Clinical Excellence (NICE) states that surgery is a treatment option for people with morbid obesity (BMI equal to or greater than 40 kg/m^2) or with a BMI equal to or greater than 35 kg/m^2 in the presence of significant co-morbid conditions that could be improved by weight loss e.g. type 2 diabetes, hypertension". Surgical techniques include restrictive procedures e.g. laparoscopic gastric banding, sleeve gastrectomy or malabsorptive procedures e.g. Roux-en-Y gastric bypass. A recent RCOG scientific opinion paper concludes that bariatric surgery improves several important markers of fertility including hyperinsulinaemia and ovulatory function. However, its potential benefits need to be balanced against the risks of surgery.

Clomifene citrate: clomifene citrate, an oral selective oestrogen receptor modulator is the first line pharmacological treatment modality for women with anovulatory infertility (WHO type 2) for over 40 years. Clomifene binds to oestrogen receptors in the hypothalamus, releasing it from the negative feedback loop and consequently leading to an increase in FSH that then leads to follicular development.

Different doses of clomifene have been used and range from 50 mg to 150 mg per day but most commonly the starting dose is 50 mg per day with 50 mg increments per cycle until a maximum dose of 150 mg per day given for 5 days. The start date of therapy is usually within 5 days of the onset of menstruation or a progestogen-induced withdrawal bleed but more commonly on day 2 of the cycle. Those who do not respond to 150 mg per day are considered to be clomifene resistant and consequently alternative treatments should be considered. Since the majority of patients who will conceive will do so in the first three months, other treatments should also be sought in those who do not conceive after 6 months of therapy.

The rates of ovulation, pregnancy and live birth over a six cycle of treatment are 49%, 30% and 23% respectively. This relatively low conception rate may be due to the peripheral antioestrogen effects of clomifene, particularly on the endometrium or due to the associated increased secretion of LH that can lead to premature leutinisation of the developing follicle.

The main side effects of clomifene are related to its anti-oestrogen effects. Centrally this can lead to symptoms such as hot flushes and uncommon but serious side effects include visual symptoms such as blurred vision, diplopia, and photosensitivity. Furthermore due to potential multifollicular development there is an 8% chance of multiple pregnancies. Another potentially serious but uncommon side effect is ovarian hyperstimulation syndrome.

- Adjuvants:

Several adjuvants including growth hormone, ketoconazole and dexamethasone have been used in addition to clomifene in an attempt to improve ovulation and pregnancy rates but mostly their use has not been supported by substantial evidence. However, metformin can be used alone or in combination with clomifene for ovulation induction in PCOS. Metformin is associated with gastrointestinal side effects include nausea, vomiting and abdominal upset. Dopamine agonists such as bromocriptine are useful if there is associated hyper-prolactinaemia.

Aromatase inhibitors: the aromatase inhibitors letrozole and anastrozole have both been used to induce ovulation. They act through the inhibition of ovarian aromatase enzyme with a consequent decrease aromatisation of androgens into oestradiol. This results in a decreased central negative feedback leading to increased FSH production. Current evidence suggests that results are similar to clomifene but with the potential advantages for letrozole over clomifene include a shorter half-life that leads to a preservation of the central feedback mechanisms and consequently monofollicular rather than multifollicular development.

The daily dose of letrozole in various studies has included 2.5 mg, 5 mg and 7.5 mg doses as well as a single 20 mg dose. However current evidence suggests that the use of the 5 mg and 7.5 mg doses offer no significant improvement in the pregnancy rates over the lower 2.5 mg dose.

Despite the effectiveness of letrozole in inducing ovulation, it must be noted that it is not licensed for this particular use. Furthermore the manufacturer states that there is a risk of fetal anomalies as shown in animal studies although so far human studies have been reassuring and have failed to show any increased risk of fetal anomalies or adverse pregnancy outcomes.

How to monitor response to treatment

Mid-luteal serum progesterone level is the most common method of measuring success of ovulation induction. A sub-optimal level indicates the need to increase the dose of the ovulation induction agent, or failure of this mode of induction if the dose is already at the maximum allowed. Commercial ovulation kits rely on serial testing of urine for evidence of LH surge.

Serial ultrasonography is an efficient method of monitoring follicular development and time ovulation in response to ovulation induction and in helping to reduce multiple pregnancy rates especially in women with PCOS who are at risk of multifollicular ovulation.

Case 2

The same patient had succeeded in dropping her BMI to 33 kg/m^2 and was commenced on a course of clomifene citrate. After 6 months she attended the clinic again as unfortunately clomifene

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