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 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; gonadotropins; meformin; ovarian drilling; 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 main categories based on the site of the lesion and as reflected by the gonadotropin profile. WHO type 1 (hypogonadotropic hypogonadism), can be caused by any lesion affecting the pituitary or hypothalamus and affecting gonadotropin production. WHO type 2 (normogonadotropic hypogonadism) is by far the commonest cause of anovulation and is most commonly caused by polycystic ovarian syndrome. Finally type 3 (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.

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Case 1

A 24-year-old woman with anovulatory infertility due to polycystic ovarian syndrome 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 polycystic ovarian syndrome (PCOS) is the commonest scenario for ovulation induction encountered in most infertility clinics. First line treatment options include the use of antioestrogens such as clomifene citrate and tamoxifen or the use of aromatase inhibitors such as letrozole.

Antioestrogens

Clomifene citrate: it is an oral oestrogen antagonist that has been used for ovulation induction in women with anovulatory infertility (WHO class 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 follicle stimulating hormone (FSH) that then leads to follicular development.

Different starting doses of clomifene have been used and range from 50 mg to 100 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 has also varied from day 2 to day 5 of the cycle. Those who do not respond to 150 mg per day are considered to be clomifene resistant and alternative treatments should be considered. Since the majority of patients who will conceive will do so in the first 3 months, other treatments should also be sought in those who do not conceive after 6 months of therapy.

Successful ovulation can be expected in around 80% of women using clomifene, however only 50% of these will conceive. 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 leutinization of the developing follicle.

Several adjuvants have been used in addition to clomifene in an attempt to improve ovulation and pregnancy rates. These include bromocriptine, ketoconazole and dexamethasone. Amongst these only dexamethasone has shown promising results.

The main side effects of clomifene are related to its antioestrogen effects. Centrally this can lead to symptoms such as hot flushes and peripherally it can lead to a potential adverse effect on the endometrium that may at least partially explain the relatively low pregnancy rates. Uncommon but serious side effects include visual symptoms such as blurred vision, diplopia, and photosensitivity. Another potentially serious but uncommon side effect is hyperstimulation syndrome. Furthermore due to potential multifollicular development there is an 8% chance of multiple pregnancies.

Tamoxifen: it is another selective oestrogen receptor modulator that can induce ovulation through a mechanism similar to that of clomifene. However unlike clomifene, tamoxifen has the theoretical advantage of having an oestrogenic rather than

antioestrogen effect on the endometrium. Despite this advantage there is no evidence so far that tamoxifen is superior to clomifene and both drugs have been found to produce similar results.

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 in aromatization 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.

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.

Case 2

The same patient attended clinic for review after a 6-month course of clomifene that did not result in ovulation despite incrementally increasing the dose to 150 mg/day. She would like to discuss further options.

Discussion

10–30% of women receiving clomifene will remain anovulatory and labelled as clomifene resistant. Options for second line treatments include the use of insulin sensitizing agents such as metformin, the use of gonadotropins or laparoscopic ovarian drilling.

Insulin sensitizing agents

The biguanide, metformin is the most commonly used insulin-sensitizing agent in this respect and has been used for some time particularly for patients with PCOS. Initial reports suggested that metformin was highly successful with reported ovulation rates as high as 46%. Based on these initial encouraging studies there was a wide interest in the use of metformin even as an alterative first line therapy to clomifene. However recent studies have led to a change in attitudes where they demonstrated the superiority of clomifene to metformin as a single first line treatment and also demonstrated no advantage to using a combination of clomifene and metformin compared to clomifene alone as first line treatment.

Consequently the use of metformin should currently be limited mainly to those with clomifene resistance as a second line treatment. Metformin may also be used to improve sensitivity to metformin in those with previous clomifene resistance.

Gonadotropins

Gonadotropins may be used as a second line treatment in patients with clomifene resistance or for those who fail to conceive despite ovulating with clomifene. There are several commercially available forms of FSH falling into two main categories, urinary (u-FSH) and recombinant FSH (r-FSH) and current evidence suggests that they are equally effective.

When administering gonadotropins for patients with PCOS it is important to note that these patients are characterized by certain factors that set them aside from other patients and need to be taken into consideration when treating them with gonadotropins. Firstly they have an increased FSH threshold, that is the critical "threshold" level needed for to stimulate follicle recruitment. Secondly they have an increased sensitivity to exogenous gonadotropins. These two factors can easily lead to ovarian hyperstimulation. To minimize the risk, a gentle stimulation regimen such as a low dose step up regimen should be used.

Complications of gonadotropin treatment

1. Ovarian hyperstimulation syndrome: a potentially serious condition characterized by shift of fluid from the intracellular to the extracellular compartment. The exact mechanism for the condition is unknown. The syndrome varies in severity form mild to moderate to severe.
2. Local allergic reactions.
3. Gastro-intestinal system disorders: nausea, abdominal pain, pelvic pain.
4. Multiple pregnancies due to multifollicular development.

Laparoscopic ovarian drilling

Laparoscopic ovarian drilling (LOD) can be used as a second line treatment to induce ovulation in women not responding to clomifene citrate. The procedure historically follows on from the earliest surgical procedure to induce ovulation in women with PCOS involving wedge resection of the ovary.

The exact mechanism by which LOD can induce ovulation in not yet fully understood. Proposed mechanisms involve an increased ovarian sensitivity to FSH, restoration of normal ovarian-pituitary feedback mechanisms leading to a decrease in baseline LH, a decrease in ovarian androgen production, and a decrease in ovarian inhibin secretion leading to increased FSH secretion.

Response to LOD has been found to be dependant on the amount of energy delivered to the ovary where ovulation rates increase with an increase in the dose of energy. Obviously this needs to be balanced against the potential harm that can result from the use of excess energy levels leading to ovarian damage. Accordingly the ideal dosage needed is in the range of 600 J/ovary.

Several factors have been found to influence the response to LOD. The presence of elevated LH and low Anti Mullerian hormone (AMH) concentrations have been associated with favourable response to LOD while the presence of an increased BMI, marked hyperandrogenism and long duration of infertility have been found to predict resistance to treatment.

Compared to gonadotropin therapy, LOD can produce similar ovulation and pregnancy rates but because it leads to monofollicular development has the advantage of being associated with a lower risk of multiple pregnancies. However the procedure is not devoid of problems. Apart from the obvious possible complications of the laparoscopic procedure such as the risk of visceral or vascular damage, LOD can be associated with the occurrence of adhesions in a significant number of patients. Furthermore there is also concern that LOD may damage the