A New Look at Ovulation

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Ovulation has an impact upon women's lives from adolescence and menarche until menopause. Many women are concerned about contraception throughout their reproductive life. When a woman presents with either abnormal uterine bleeding or with infertility, it is time to consider whether ovulation is occurring normally. With unexplained infertility when there is no apparent problem with ovulation, manipulating the timing and number of ovulations are a part of therapy.

What's new about ovulation?

Recent landmark research has shown that the old way of considering follicle growth and ovulation in women will be surpassed by the documentation of the growth of multiple waves of follicles.[1,2]

In the past, the menstrual cycle was traditionally described as a 28 day cycle where follicle stimulating hormone (FSH) caused a single wave of follicles to grow; a single follicle was selected to continue growth, then to ovulate (on day 14) when a high level of estrogen induced a surge release of luteinizing hormone (LH).[3] The site of ovulation became a corpus luteum gland capable of progesterone secretion which regressed in the absence of conception.

The work of Pierson and Baerwald has shown that two and three waves of follicle growth preceded ovulation in ovulating women with regular menstrual cycles (24 to 34 day cycle lengths).[1,2] A new group of growing follicles emerged with each wave. Women with two waves had an initial wave of anovulatory fol-

Amy's case

Amy is in your office relating the story of her reproductive life. When she was a teenager, she had unpredictable heavy periods. They began to be more regular, but were painful. Her family physician recommended using oral contraceptive pills (OCs), which she used for many years. She later required contraception, so she continued using the OCs for many years until she wanted to conceive. When she stopped the OCs, she waited four months for her next period, but she was not pregnant. Pregnancy did not occur, as hoped, during the next three years, despite her appreciation of family planning methods including her use of basal body temperature recording and her self-assessment of mucus changes.

Amy and her partner have been assessed in the local infertility clinic, and so far there is no explanation for their infertility.

For preliminary tests, see page 132.

licles emerging in the preceding luteal phase, where a dominant follicle grew then regressed in approximately 40% of cycles and no dominant follicle was seen in 60% of cycles; a second wave of follicles emerged in the early follicular phase followed by selection and growth of a dominant follicle that progressed to ovulation. When women had three waves, there were two waves of anovulatory follicle growth followed by a third wave that progressed to ovulation; again in about 40% of cycles a dominant anovulatory follicle was selected then regressed at the time when a new wave of follicle growth occurred. Also, seven of the 63 women failed to ovulate at all, even though they had a history of regular menstrual cycles, and had ovulated during their pre-study cycle.

Although it was not the mandate of the study to observe women with cycles longer than 34 days, more than three waves were observed, and ovulation occurred in the final wave. In 6% of cycles, the maximal size of the dominant follicles in anovulatory waves mimicked the large size of a typical dominant follicle that could have progressed to ovulation; it is apparent that there is a yet to be an explained mechanism to support the regression of some dominant follicles and permit the growth and ovulation of other dominant follicles.

How is ovulation monitored?

High resolution transvaginal ultrasonography (TVUS) is a rapid non-invasive way to observe daily follicle growth and ovulation.[3,4] With ovulation induction, TVUS is used to monitor follicle growth so that human chorionic gonadotropin (hCG) can be given in place of LH when dominant preovulatory follicle(s) reach approximately 18 mm. Ovulation can be syn-

Table 1
Available ovulation inductions

Gonadotropin releasing hormone	• Pulsatile delivery by intravenous pump • Used when follicle stimulation hormone (FSH) and luteinizing hormone (LH) levels are low (hypothalamic replacement) • Depot form given to suppress LH surge during FSH therapy for in vitro fertilization (IVF)
Clomiphene citrate (CC)	• 1 to 2 tablets daily for 5 days to induce ovulation • Trial of 10 days, or higher doses up to 5 tablets for failure of ovulation
FSH	• Daily injections for 8 to 12 days, low-dose to induce ovulation when CC fails to induce ovulation • Medium dose to induce multiple ovulation for unexplained infertility after failure of CC to create pregnancy • Medium or high-dose of IVF to retrieve multiple oocytes
Human chorionic gonadotropin	• Single injection to induce ovulation in place of LH surge at known time • Used with CC and FSH[3,6,9,12]

Amy's tests

Preliminary tests reveal:

- A regular menstrual cycle with biphasic temperature charts
- Elevated luteal phase progesterone levels
- Normal sperm numbers and motility
- No anatomic causes are revealed with normal hysterosalpingography, reproductive pelvic ultrasound examination and diagnostic laparoscopy.
- Day 3 follicle stimulating hormone (FSH) levels were normal

What are the therapeutic options for Amy? See page 134.

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chronized with either sperm insemination or oocyte retreival for in vitro fertilization. Thus, anovulatory follicles have thin, sharply demarcated follicle walls; ovarian hyperstimulation syndrome can be monitored.[4] Endometrial thickness and pattern (A to D) seen with TVUS are related directly to preovulatory follicle growth and estrogen secretion and progesterone secretion following ovulation.[3,4] If the endometrium fails to achieve adequate thickness and pattern, aberrant follicle quality can be suspected even if follicles grow.

When is ovulation therapy required?

Induction of ovulation is reasonable for any woman who wants to conceive and who does not have regular menstrual cycles. Regular cycles imply that ovulation is occurring. Chronic anovulation is undesirable because of the risk of dysfunctional uterine bleeding and endometrial neoplasia.[5,6] However, women who are apparently ovulating may also consider using fertility enhancement therapy. Induction of multiple ovulation combined with intrauterine sperm insemination or in vitro fertilization (IVF) may be used if infertility is prolonged.[7-9]

How is ovulation therapy completed?

GnRH replacement mimics the normal hypothalamic release and stimulates the pituitary to synthesize and release FSH so that follicle growth can occur.[7,9] Not all individuals respond to this therapy, so that TV US should be used to monitor follicle growth and ovulation. FSH is often used instead of GnRH therapy because the costs are equal, response to GnRH is variable. However, GnRH therapy typically results in single ovulation, whereas FSH can result in multiple ovulation, multiple pregnancy, and ovarian hyperstimulation.

For anovulatory women with polycystic ovary syndrome (PCOS), lifestyle modifications to lose weight along with use of an insulin sensitizer (metformin) is the first therapeutic option.[4,11,12] Metformin decreases insulin resistance that causes excess ovarian production of androgen and anovulation. Ovulation and regular menses may begin within three months of therapy. If conception does not occur, clomiphene citrate (CC) is prescribed along with the insulin sensitizer.

CC is an antiestrogen that acts on the hypothalamus and pituitary, causing a synchronized pituitary release of FSH.[4,11] CC can induce synchronized follicle growth; single or multiple ovulation follow the release of LH. CC is combined with hCG if follicle growth occurs without an endogenous LH surge[4,7] or to synchronize the timing of ovulation with the insemination of sperm.[14] TVUS is used to time hCG, assess ovulation, and to ensure an adequate endometrial growth response. If ovulation does not occur, the dose of CC can be increased

Amy's therapeutic options

Therapeutic options included ovulation induction using either clomiphene citrate (CC) or follicle stimulating hormone (FSH) and human chorionic gonadotropin (hCG), along with intrauterine insemination of sperm (IUI), and in vitro fertilization. Alternatively, this couple could choose to approach adoption. They have also considered remaining child-free should they be unable or unwilling to approach the other alternatives.

Amy and her partner chose to complete ovulation therapy with IUI. After 4 treatment cycles with CC/hCG/IUI, and one cycle of FSH/hCG/IUI, Amy conceived and delivered twins. In her early forties, she had complaints of hot flushes and difficulty sleeping.

She and her family physician discuss the possibility of hormone replacement therapy for perimenopause and the possibility of early menopause.

Table 2
Ovarian hyperstimulation syndrome

- Ovarian hyperstimulation syndrome (OHSS) occurs in up to 25% of ovulation induction cycles.
- It is more common following follicle stimulation hormone induction of ovulation for women who are anovulatory.
- Severe OHSS presents in 0.1-10% of cycles with ascites and pleural effusion, and hypercoagulability from intravascular hemoconcentration.
- It resolves within approximately 10 days, but is prolonged when pregnancy coexists.
- OHSS generally resolves by the end of the first trimester of pregnancy.
- Therapy is aimed at fluid hydration to prevent hemoconcentration and hypercoagulability. Paracentesis is used to ease the discomfort of ascites, and infusion of intravenous protein to restore intravascular fluid volume.

or extended for 10 days followed by hCG self-injection. Another alternative for resistance to clomiphene is to pretreat with an oral contraceptive pill for approximately 42 days before using CC.[13]

Intrauterine insemination (IUI) has been shown to substantially increase conception when used with ovulation induction for couples with anovulation, unexplained infertility, and reduced motile sperm.[15] IUI is recommended to offset the antiestrogenic effect of CC.[11,16] The higher the dosage of CC, the higher the risk of antiestrogenic effects, including scant cervical mucus and reduced growth of the uterine endometrium, both which may decrease the chance of sperm transport and conception.[11,16] Other side-effects from CC include hot flushes and transient visual disturbances. Multiple ovulation can result in multiple pregnancy (usually twinning), which is similar to the rate in the general population. Lifetime use of CC is limited to 12 cycles because of an epidemiologic report that linked prolonged (years) use of CC to a higher incidence of ovarian cancer.[16]

FSH is used when clomiphene fails to induce follicle growth/ovulation or when ovulation following CC therapy fails to result in conception.[4,11,17] FSH is self-injected daily (im or sc) for an average of 10 to 14 days; FSH dosage is titrated to increase or decrease the number of growing follicles. TVUS and estradiol levels are used to assess follicle growth. With PCOS, an excessive number of follicles are available that can grow, and response to FSH is unpredictable. To decrease the number of growing follicles a low dose of FSH is used. If low-dose FSH results in no follicle growth, but higher dosages allow too many follicles to grow, there is a risk of multiple ovulation and Ovarian Hyperstimulation Syndrome. One alternative is to cancel ovulation therapy, or withhold insemination to prevent conception. A new alternative is to convert therapy to IVF, so that oocytes are removed from the ovaries, fertilized in vitro and a limited number of embryos (typically one to three embryos) are transferred back to the uterus during the early luteal phase of the cycle. Extra embryos can be cryopreserved for later use. If the risk of OHSS is high, all embryos are cryopreserved until OHSS resolves and embryo transfer is delayed.

In couples with unexplained infertility or low motile sperm counts, IUI has been demonstrated to substantially increase conception when used with

induction of multiple ovulation. Without ovulation therapy, IUI does not increase conception.[19] CC/hCG/ IUI used for three to six cycles provides a 3% to 12% pregnancy rate per cycle.[18] Detection of urinary LH can replace hCG to time IUI without apparent compromise of the pregnancy rate; however, this cost-saving method fails to assess the endometrium and multiple follicle growth. In some women, CC does not cause multiple ovulation.[19] When CC/hCG fails to initiate pregnancy or when ovulatory dysfunction is revealed, FSH/hCG is used to induce multiple ovulation (ideally two to five ovulations per treatment cycle).

For unexplained infertility, the chance of pregnancy with FSH/hCG/IUI is reported at approximately 13% to 35% per cycle with a multiple pregnancy rate of 25%, an ectopic pregnancy rate of approximately 5%, and severe OHSS developing in 0% to 1%.[20] A randomized controlled trial of recombinant LH (rLH) or hCG for FSH induction of ovulation for unexplained infertility resulted in a clinical pregnancy rate of 25% to 38% for various doses of rLH compared with 25% for the hCG group.[15,18,19] However, recombinant LH is not yet available for clinical use. It has been recommended that controlled ovarian hyperstimulation/IUI be limited to three cycles; if more therapy is acceptable, the next option is to complete IVF therapy.[6,7,15,21] High dose GnRH is used to suppress a LH surge and FSH/hCG induction of ovulation is used to produce multiple follicle growth so that numerous oocytes can be retrieved and fertilized in vitro.[5,15,19,20] IVF can therefore test whether fertilization occurs. One to three embryos are transferred to the endometrial cavity and extra embryos can be cryopreserved for later use.

Does age change ovulation?

The decline in fertility with advancing age of women (over 35 years) has led investigators to look for predictors of fertility potential.[15, 17,21,22]

Giving FSH at supraphysiologic levels for many days, starting in the early follicular phase, will allow follicles that typically would undergo atresia, to grow; follicles can then be induced to ovulate with LH or hCG.[4,16] However, follicle growth is governed by the pool of resting follicles. An overall reduction in ovarian oocytes that normally occurs at perimenopause is linked with a poor response to FSH stimulation and an apparent increase in resting follicles, as seen with PCOS is linked to a vigorous response to FSH stimulation.[16]

Compared with high responders, women with a poor follicular response to FSH induction of ovulation, (that is poor responders), had fewer follicles reaching a preovulatory size even with excessively high dosages of FSH, less embryos with IVF, and lower pregnancy rates when apparently normal quality embryos were transferred with IVF therapy.[17,22]

Day 3 FSH levels in unstimulated menstrual cycles of poor responders were higher than 15IU/L. Hence, when basal day 3 FSH levels rise above 10, aggressive ovulation therapy may indicate, whereas levels above 20 may lead clinicians to recommend that no therapy be offered or that success with aggressive therapy would likely be very poor. Even if preovulatory size follicles grow in response to FSH and hCG is given, there is no guarantee that an individual follicle will ovulate or will contain a competent oocyte capable of fertilization or embryonic growth.[22] An age related pregnancy rate can be observed with IVF.

In Canada, the overall pregnancy rate following 5,188 IVF treatment cycles in 17 centres in 2001 was 28% per cycle of started therapy for all etiologies of infertility; two thirds were singleton pregnancies, and the majority of multiple pregnancies were twins.[23] The pregnancy rate was highest for women under 35 years at 34%. It was 28 % for women 35 to 39, and 15% for women 40 or over.

What are the risks from ovulation therapy?

Negative effects of ovulation therapy include OHSS, multiple pregnancy, and ectopic pregnancy (5%).[7,15,25] The frequency of multiple pregnancy following multiple ovulation has been reported at 5 to10% with CC and approximately 25 % after FSH therapy. With FSH therapy, high order multiple gestation is possible, especially if anovulation is the etiology of infertility.[7,9,11] Restriction of the number of embryos transferred with IVF and reduction of the number of spontaneous ovulations with IUI therapy will decrease the multiple pregnancy rate, but also lower the pregnancy rate. Multifetal selective reduction is an option available for multiple gestation of high order.[24] However, it is preferable to prevent the occurrence of high order multiple gestation, which is now possible by converting ovulation/IUI therapy to IVF, and by limiting the number of embryos transferred.

Take-home message

- When a woman presents with either abnormal uterine bleeding or infertility, it's time to consider whether ovulation is following a normal pattern.
- Couples with unexplained infertility or reduced motile sperm can use clomiphene citrate (CC) for follicle stimulating hormone (FSH) to induce single or multiple ovulation.
- CC use is restricted to 12 cycles a lifetime, due to an epidemiologic association with ovarian cancer.
- Couples with unexplained infertility and anovulation using CC or FSH can substantially increase the chance of conception by using intrauterine insemination.
- Multiple gestation is low after CC, approximately 25% after FSH therapy.
- Multiple pregnancy of high order can be prevented with in vitro fertilization so that multifetal selective reduction can be avoided.

What is OHSS?

The exact etiology of OHSS is unknown[7,15,25] (Table 2).

OHSS is seen after ovulation, and is characterized by increased capillary permeability which leads to a fluid shift of protein-rich fluid from the vasculature. This results in the formation of multiple large ovarian cysts. Mild OHSS follows 8% to 23% of cycles. Severe OHSS presents in 0.1% to 10%. Modalities to decrease OHSS include monitoring therapy with TVUS and estradiol levels, and titrating the dosage of FSH to restrict the growth of excessive numbers of follicles. Oocyte retrieval with IVF will likely decrease the severity of OHSS, but has not prevented its occurrence.

What are the determining factors for choosing ovulation therapies?

Therapies are chosen to provide the least amount of disruption of life at the lowest possible financial, time and emotional costs.[8,9] When tests have demonstrated tubal patency and adequate concentration of motile sperm and the mechanism of anovulation or presence of ovulation has been confirmed, fertility enhancement therapy, induction of multiple ovulation with IUI can be considered. Typically, CC therapy is considered before FSH, and IVF is considered last.

When advising patients, the chance of attaining a pregnancy with therapy and the costs should be disclosed. The woman's age should also be considered in the context of each therapy for each individual etiology of infertility. Risks of attaining a multiple gestation and OHSS must be disclosed. Indicators to predict cessation of fertility potential (at any age but especially over 35) such as day 3 FSH levels, may be helpful to direct more or less aggressive and costly therapy. One can consider the chance of pregnancy per cycle with the various therapies. Approximately 3% to 12% for CC/IUI, 13% to 35% for FSH/IUI and 15% to 34% for IVF.[8,14,18,19,23] The average Canadian cost of therapy ranges between $250 and $500 for CC/IUI, $1, 200 to $4, 000 for FSH/IUI ,and $7,000 to $14,000 for IVF. The discussion to consider therapy should be based upon what financial resources are available to the infertile couple, as well as their ability to accept the use of technology to conceive.

In the past, ovulation therapy was reserved for anovulatory women, and IVF was considered only for tubal obstruction. It has been shown that normal ovulating women can present with unexpected cycles of anovulation. Anovulation or aberrant ovulation may be more common in infertile couples with unexplained infertility than was previously recognized. Now both ovulation therapies with IUI and IVF are realistic options for many etiologies of infertility. However, the reason and timing for choosing each option may vary for women of differing ages and etiologies of infertility. The economic burden of fertility therapies will also direct what options can be used. We can expect that research will improve our understanding of ovulation and provide more effective therapies in the future. CME

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