Progress in understanding human ovarian folliculogenesis and its implications in assisted reproduction

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Abstract

Purpose To highlight recent progress in understanding the pattern of follicular wave emergence of human menstrual cycle, providing a brief overview of the new options for human ovarian stimulation and oocyte retrieval by making full use of follicular physiological waves of the patients either with normal or abnormal ovarian reserve.

Methods Literature review and editorial commentary.

Results There has been increasing evidence to suggest that multiple (two or three) antral follicular waves are recruited during human menstrual cycle. The treatment regimens designed based on the theory of follicular waves, to promote increased success with assisted reproduction technology (ART) and fertility preservation have been reported. These new options for human ovarian stimulation and oocyte retrieval by making full use of follicular waves of the patients either with normal or abnormal ovarian reserve lead to new thinking about the standard protocols in ART and challenge the traditional theory that a single wave of antral follicles grows only during the follicular phase of the menstrual cycle.

Conclusions The understanding of human ovarian folliculogenesis may have profound implications in ART and fertility preservation. Further studies are needed to evaluate the

optimal regimens in ART based on the theory of follicular waves and to identify non-invasive markers for predicting the outcome and the potential utilities of follicles obtained from anovulatory follicular waves in ART.

Keywords Human ovarian follicular waves · Assisted reproduction technology (ART) · Ovarian stimulation · Synchronization of antral follicles · Luteal phase oocyte retrieval

Introduction

The ovary is an extremely dynamic organ. Ovarian follicular growth and regression are complicated physiologic phenomena which have been of interest to researchers and clinicians for decades. Current knowledge on human ovarian follicular dynamics is based on the synergistic use of histologic, endocrinologic and ultrasonographic approaches [1–3]. Particularly, high-resolution trans-vaginal ultra-sonography is a very effective method of monitoring ovarian follicular growth in women [4]. The emergence of 2–5 mm follicles has been detected histologically and ultra-sonographically throughout the human menstrual cycle [5] and it has been recognized as the recruitment of antral follicular waves only in follicular phase by many researchers for years [6, 7]. However, the pattern of follicular wave emergence is a long-standing debate. There has been increasing evidence to suggest that multiple (two or three) antral follicular waves are recruited during the menstrual cycle [8, 9]. In other words, antral follicular growth may start in different phases of the menstrual cycle due to the balance of endocrine and intra-ovarian regulators [7], which differs from what was previously thought.

Ovarian follicle development is tightly regulated by crosstalk between cell death and survival signals [10].

Capsule Progress in understanding human ovarian folliculogenesis leads to the new thinking of the options for human ovarian stimulation and oocyte retrieval of the patients either with normal or abnormal ovarian reserve, which may promote increased success with ART and fertility preservation.

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Depletion of the ovarian follicular reserve starts during fetal life and continues throughout a woman's life span. Only a small proportion of the primordial follicles will reach the ovulatory stage, while the rest follicles will undergo the degenerative process called atresia [11]. In a natural menstrual cycle, there is only one follicle will be chosen to ovulate eventually while others going atresia under the accurate regulation of both hypothalamus-pituitary-ovary axis and intra-ovarian regulators, such as growth factors, cytokines and gonadal steroids [12]. However, in the controlled ovarian stimulation of current assisted reproduction technology (ART), the hypothalamus-pituitary-ovary axis is interfered and partially controlled by using medicine. For example, the desensitization and down-regulation of pituitary through GnRH-agonist long protocol makes it possible to initiate exogenous gonadotropins on the day of expected wave emergence [13, 14]. Moreover, the manipulation by administration of exogenous gonadotropins may have the selection occur more than once in a menstrual cycle. The knowledge of human ovarian follicular waves, which challenges the traditional theory that a single wave of antral follicles grows only during the follicular phase of the menstrual cycle, will have profound implications in the practice of ART.

The purpose of this review is to highlight recent progress in understanding the pattern of follicular wave emergence of human menstrual cycle, provide a brief overview of the new options for human ovarian stimulation and oocyte retrieval by making full use of follicular physiological waves of the patients either with normal or abnormal ovarian reserve.

Theories of follicular waves

Follicular development occurs in a wave-like pattern in most domesticated animal species [15–17] and in humans [8, 9] during the estral/menstrual cycle. The decrease of luteal estradiol and inhibin A following regression of corpus luteum leads to a transient rise of serum FSH, thus, follicle recruitment is induced [18]. However, if wave emergence truly occurs only once in the late luteal phase or early follicular phase after luteolysis, and follicular development is indeed limited by the inhibitory effects of luteal progesterone as our previous notion have been questioned. Baerwald and his colleagues have documented a new understanding for the waveform of ovarian follicular development during the human menstrual cycle [9]. In the researches, the number of follicles which are no less than 5 mm and the alterations in diameter of every single follicle which is no less than 6 mm were observed by daily performing transvaginal ultrasonography during the interovulatory interval (IOI) in 50 women, who have a history of regular menstrual cycles without medications known to interfere with reproductive function. It was demonstrated

that 34 of the 50 women (68 %) exhibited two waves of follicle development; the remaining 16 women (32 %) presented three waves. In all 50 women, the final wave of the cycle was ovulatory and the preceding waves were anovulatory. None of the women evaluated exhibited only a single wave during the IOI. Furthermore, Women with three follicular waves per cycle have 2-days longer IOI (29 days), which was significantly different from that in the women with two waves (27 days). It was also indicated that an anovulatory wave emerged at the time of ovulation (day 0) followed by emergence of the ovulatory wave during the early-follicular phase in women with two follicular waves. While in women with three waves, the first anovulatory waves emerged at day 0 and the second anovulatory wave emerged during the mid-to late- luteal phase followed by the third wave (the ovulatory wave) emerged in the early- to mid-follicular phase [9].

In addition, repeatability of 2-wave and 3-wave patterns of ovarian follicular development has been examined in several animal species, such as mares [15], cattle [16, 17, 19–21], wapiti [22], sub-human primates [23]. Some animal studies have been demonstrated recently that the duration of the IOI was predictive of the wave pattern (2-wave or 3-wave) (Table 1), and that the wave pattern possess a propensity to be repeatable among individuals. Taking the bovine estrous cycle for example [21], it was reported that the 2-wave pattern was detected in 68 % IOIs (62 out of 91), and the 3-wave pattern was detected in 32 % IOIs (29 out of 91) in bovine estrous cycle. The percentages above are exactly the same with what detected in human [9]. It was also surprising to notice that the majority (88 %) of IOIs which were less than 21 days was of the 2-wave pattern, whereas the majority (78 %) of IOIs which were no less than 22 days was of the 3-wave pattern. The repeatability of wave pattern and the proportion of two- versus three-wave patterns within the herd were not influenced by the season of year [21]. Those several lines of evidence suggested that the 2 or 3 wave pattern can be repeatable almost at any estral cycle of the same individual and is related with the length of IOI, which are in high accordance with the circumstances observed in human [8, 9]. Moreover, results of studies were also supportive of the hypothesis of a regulatory role of the dominant follicle of Wave 1 on the wave pattern [21]. However, more studies with larger sample size in human as well as the researches about the molecular and cellular mechanism of the recruitment of antral follicles in this wave pattern are needed.

Another study also by Baerwald showed some more characteristics about follicular waves and about women exhibiting major or minor wave patterns of follicle development during IOI [8]. Major waves were defined as those in which one follicle grew to no less than 10 mm and exceeded all other follicles by 2 mm at least. Minor waves

Table 1 Characteristics of wave patterns in animal/human studies [9, 20–22, 24]

	Species	IOIs predict wave pattern	Repeatability	Percentage of 2 or 3 waveforms	Wave emergence day			
					1st wave	2nd wave (2-wave)	2nd wave (3-wave)	3rd wave
Jaiswal et al. [21]	Bovine	Y ^a	Y	100 %	0	NM ^b	NM	NM
Baerwald et al. [9]	Human	Y	NM	100 %	0	14	12	18
McCorkell et al. [22]	Wapiti	Y	NM	85 %	0	10	9	16
Jaiswal et al. [20]	Heifer	Y	NM	100 %	0	9	9	17
Malhi, 2005	Cows	Y	Y	100 %	0	10	9	16

^a Y yes; ^b NM not mentioned

were defined as those in which follicles developed to a diameter of no more than 10 mm and follicle dominance was not manifest. There were totally five different patterns were observed concerning the condition of major-minor wave, with no exception that the last waveform must be a major wave (ovulation). However, both in 2-wave and 3-wave women, it seems that the preceding anovulatory waves can be either major or minor waves [8]. Indeed, whether in anovulatory waves or ovulatory waves, the loss of dominant follicle is accompanied by decreased levels of hormones synthesized by the follicle, such as oestrogen and inhibin. Hormones dropping then result in a temporary increase of FSH secretion by the pituitary gland through a negative feedback mechanism. In consequence, the rise of FSH level is thought to be responsible for preventing atresia of next cohort of 2–5 mm antral follicles [25].

So a question rose here: how can an antral follicular wave be emerged if its preceding wave is a minor wave? Moreover, it was noticed that there will always be a major wave following the regression of a major wave, while it can be either major or minor wave following a minor wave. Thus, we have held the hypothesis that the minor waves may be regulated mostly by hypothalamus-pituitary-ovary axis; meanwhile the major waves may be affected both by hypothalamus-pituitary-ovary axis and intraovarian regulators. Additionally, major waves may play a role in influence intraovarian paracrine directly or indirectly.

Synchronization of follicular development

Documentation of a wave phenomenon of ovarian follicular development provides women undergoing assisted reproduction with better timing for initiating ovarian stimulation protocols. Synchronizing antral follicles in ovarian stimulation regimens may increase cohort of mature follicles and produce more competent oocytes, thereby enhance ART efficiency. Different strategies for synchronizing follicles in controlled ovarian hyperstimulation (COH) protocols

reported: (1) suppressing the natural increase in FSH level during the luteofollicular transition with medicine; (2) increasing circulatory FSH concentration with short-acting gonadotrophin-releasing hormone agonist (GnRHa) or mini dose exogenous gonadotrophin before initiating ovarian stimulation with conventional dose of gonadotrophin.

Because of the variable sensitivity of follicles to FSH, the FSH rise during the late luteal phase may lead to advanced growth of the few, more sensitive follicles and ultimately result in a smaller follicular cohort available for recruitment. Fanchin R et al. [26] described suppressing the natural increase in FSH level during the luteofollicular transition with estrogen administration to improve follicular synchronization and possibly improve oocyte yield in COH cycles. This prospective study recruited 90 IVF candidates who were randomly pre-treated with 17 β -E₂ (4 mg/day) from day 20 until day 2 of next cycle (E₂ group, $n=47$) or placebo (control group, $n=43$). The result showed that follicles were smaller (9.9 ± 2.5 versus 10.9 ± 3.4 mm, $P<0.001$) with size discrepancies attenuated ($P<0.001$) in the E₂ group compared with that in the control group on day 8. The authors concluded that E₂ administration during luteal phase reduced the pace of growth, improved size homogeneity of antral follicles on day 8 of r-FSH treatment, and increased the number of follicles reaching maturation at once. Moreover, patients with E₂ pre-treatment were found to have a decreased cancellation rate, an increased number of oocytes retrieved and fertilized, and an increased number of embryos transferred [27]. Estradiol pre-treatment protocols improved ovarian responsiveness and this may lead to an increase in pregnancy rate in poor responders [28].

However, in some studies, the results did not show advantage with the luteal estradiol pre-treatment before gonadotropin stimulation in IVF treatment. For example, a retrospective study observing the oocyte yield with the luteal estradiol patch in anticipated poor responders found that estradiol was ineffective regarding follicular synchronization and increasing oocyte yield, which indicated that the protocol could not be expected to increase follicular

recruitment [29]. Oral contraceptive pills (OCPs) are also widely used to control FSH rising in luteal phase. It was considered that OCP pre-treatment in IVF cycles is beneficial in improving ovarian responses by inhibition of intrinsic gonadotrophins before ovarian stimulation [30]. In addition, GnRH antagonist administration during the same period has also been reported to synchronize follicular growth [31]. While a retrospective study showed that synchronization of follicular wave by using E_2 and GnRH antagonist in luteal phase is not superior to E_2 alone in low responders undergoing ovarian stimulation before IVF [32]. A meta-analysis [33] demonstrated that the number of oocytes retrieved and mature oocytes were significantly higher in luteal estradiol pre-treatment protocols than the standard protocols in poor responder. The limitation of this meta-analysis is the lack of a uniform definition of “poor ovarian responders”, which leads to the difficulty of comparing IVF outcomes with different protocols. Furthermore, most of the studies were concerned about poor responders not the normal women. Up to now, the effect of suppressing luteal phase FSH by using medicine to attain synchronization of follicular development before initiation ovarian stimulation is still conflicting. It is necessary to conduct the prospective randomized clinical trials with larger sample sizes to evaluate the effect of these protocols.

Another strategy has been demonstrated that minor “flare up” effect of daily GnRHa before initiation ovarian stimulation can improve the synchronization of follicular development. Wang’s [34] observation showed that the FSH level rose slightly right after daily GnRHa administration even on the 10th, 15th, 18th day of GnRHa administration and the percentage of the follicles in diameter of 4.5–7.0 mm increased while the percentage of the follicles in diameter of 3–4 mm decreased at 15th day comparing with those at 10th day. There was no change of the percentage of the follicles in the diameter of 7.5–10 mm at different time. It was concluded that minor ‘flare up’ effect of daily GnRH-a administration may improve the synchronism of follicular development.

Wang et al. [34] interpreted their results that GnRHa can down-regulated the expression of AMH of follicles with a diameter ≤ 4 mm and enhanced the sensitivity to FSH. In addition, the ‘flare up’ effect of GnRHa results in a slightly rise of endogenous FSH level that may drive the follicles in diameter ≤ 4 mm to grow. At the mean time, the elevated FSH concentration was below the threshold which allowed the follicular cyclic recruitment so that the follicles with diameter of 7.5–10 mm could not start development. Consequently, daily GnRHa administration may synchronize the antral follicle cohort at the meantime of down regulation of pituitary. Divergence occurs when the dominant follicle reaches a diameter of 10 mm on Day 6–9 of the follicular phase in women [8].

Before follicles develop to selection procedure the effect of gonadotrophins on the cascade of follicular development

events is further complicated by the ovarian production and secretion of factors modulating gonadotrophin activity on a cellular level. These local modulators include AMH and inhibin B both secreted by granulosa cells. The granulosa cells of secondary, pre-antral and small antral follicles, with the diameter < 4 mm, expressed AMH highest [35]. Intra-follicular AMH gradually decreases during antral follicular growth until 8–10 mm (i.e. approximate time of selection). When AMH expression diminishes and ultimately becomes undetectable, FSH-dependent follicular growth has been initiated [35, 36]. Therefore, AMH inhibits the initiation of primordial follicle growth from the ovarian reserve [35, 37]. In contrast to AMH, all follicles of the cohort produce inhibin B, which contributes to the decrease in FSH that occurs prior to selection [38]. Follicular fluid inhibin B peaks at a follicle diameter of 9–10 mm in women [39].

Base on the evidence of Wang’s study of increasing endogenous FSH concentration by daily GnRHa, a hypothesis may be supposed that some early antral follicles are able to respond to lower amounts of gonadotrophin which is under the threshold of cyclic recruitment, so that mini dose exogenous gonadotrophin may synchronize the antral follicle growth before initiating ovarian stimulation. A pilot study is being conducted [He ZY, Yang DZ, et al.: unpublished data] to evaluate the effect of low dose human menopausal gonadotropin (HMG) on synchronization of follicular wave emergence in women undergoing long protocol IVF. The patients were prescribed 75 iuHMG intramuscular injection every other day for twice from the 14th day of down-regulation. The diameter of every follicle on the days before and after HMG administration was measured. The preliminary results with increasing percentage of the follicles with diameter of 5–6 mm after HMG administered and increasing the number of oocyte retrieval have been encouraging.

The hypothesis of slightly increased endogenous or exogenous gonatropin level improving synchronization of antral follicles needs to be proved theoretically and clinically. It is unclear whether paracrine or autocrine factors are involved. Further study is needed to clarify: (1) the optimal dose of pretreatment gonadotropin which is enough to drive antral follicle synchronic growth while is under the threshold of cyclic recruitment; (2) the timing initiation of exogenous gonadotropin for ovarian stimulation; (3) the diversity of the sensitivity to gonadotropin in follicles in different diameter or stage; (4) the factors of paracrine or autocrine involved in the procedure of synchronization.

The follicular recruitment in human luteal phase

The traditional theory had the notion of luteal inhibition of antral follicular development and that a single cohort of

follicular wave grows only during the follicular phase of the menstrual cycle. Earlier study showed that the most of luteal phase follicles in women were atretic [40], while follicular atretic situation in the luteal phase has been thought to be the result of the inhibitory effects of luteal progesterone production [8, 40]. It was suggested that follicular development in the luteal phase represented an abnormal reproductive event [1].

The theory of multiple follicle waves during the human menstrual cycle has challenged the traditional notion [38]. Using oocytes obtained from 15 donors wearing a progestin-delivering IUD or subcutaneous implant compared with that from 111 routine donors, ovarian response to controlled ovarian hyperstimulation (COH) had not be altered by progestin released from IUD or implant [41].

In several case reports, women scheduled for COH-IVF presented with multiple follicles development and high E2 levels within or after 2 weeks of GnRH agonist daily administration during the mid or late luteal phase [42–44]. It was reported that the retrieval of mature oocytes in luteal phase and embryo were obtained [42–44], as well as two pregnancies with the delivery of healthy infants [43, 44]. The possible explanation could be that recruitable follicles were present in luteal phase despite the presence of a functioning corpus luteum and increased levels of P. These follicles were able to respond to the “flare-up” of FSH produced by the GnRH-a and progress into mature follicles within 14 days [43].

In vitro maturation (IVM) of oocytes and oocyte retrieval has become one of the options for fertility preservation in cancer patients. This procedure is usually performed during the follicular phase. However, several studies have reported non-follicular phase oocyte retrieval. Cha et al. [45] showed that immature oocytes obtained during various gynecologic surgeries at different times of the menstrual cycle matured in vitro and could be fertilized. Pregnancy was reported after donated oocytes during cesarean section [46]. Observations confirmed that oocytes obtained during the luteal phase of cancer patients have the capability to mature in vitro and fertilized [47, 48]. These data supported the hypothesis that viable antral follicles exist during the luteal phase, which proposed by Baerwald et al. [8].

It has being tried that ovarian stimulation initiates on early luteal phase in infertile women with reproductive aging, who had had cancelled cycles because failed getting oocyte or embryo by standard IVF protocol previously. Mini-stimulation or natural cycle protocols were applied in the follicular phase, and ovarian stimulation was restarted 1 day after oocyte retrieval or ovulation. It was demonstrated that competent oocytes, good quality embryos were obtained and there have been a few clinical pregnancies after frozen-thawed embryo transfer [Li Y, Yang DZ, et al.: unpublished data]. For women of reproductive ageing, this approach is with following advantages: i) more options and

chance to harvest oocytes at the limitation of ovarian reserve; ii) no worry about the occurrence of premature endogenous LH surge; iii) less cost for COH compared to conventional protocols.

Further clinical and experimental studies are needed due to very limited data available and small sample size observed up to now. It is essential to clear cut differences between oocyte retrieved during follicular phase and luteal phase on the aspects of genetics, biochemistry, metabolism, morphology and potential developmental competence.

Prospective research directions

Clearly, there is sufficient overlap when concerning the comparative aspects of follicular wave patterns in demonstrated animal species and in human. The similarities included emergence of the future dominant follicle before largest subordinate follicle, length of intervals, percentage growth of follicles in a cohort, incidence of major anovulatory waves during IOIs, et al. [15–17, 19–21]. Similar follicle dynamics between human and large animal models indicate animal species can be a useful experimental model for study of folliculogenesis in women, with the advantage of larger follicle size.

The studies of follicular dynamics done in large animals indeed support the wave theory of antral follicle development during the menstrual cycle in human. On the other hand, so far, it has not been established whether follicular wave dynamics are consistent within individual women, related with fertility, or change with age, and, crucially, influence outcomes in ART. Moreover, further evaluations need to be performed to determine the role of human pituitary gonadotropins and ovarian steroid hormones in the development of ovarian follicular waves.

The increasing knowledge of human ovarian follicular waves opens new avenues for future reproductive related practice and research. There are still long way to go before conclusions may be drawn. Studies must be performed on women in variable situations such as different age, BMI, ethnicity, ovarian dysfunction, broader demographic profiles. Further research is essential for understanding the physiologic, biochemical and molecular mechanisms underlying the human ovarian follicular dynamics. Randomized controlled studies with relatively large sample size are needed to evaluate the optimal timing, dose, duration of exogenous gonadotrophin administration in ART based on the theory of follicular waves so as to enable more time-efficient and less expensive protocols of ovarian stimulation.

The investigations into follicular dynamics should also aim to enable optimal utilization of the hitherto untapped potential of ovarian reserve follicles and circumvent the limitations of reproduction under physiological conditions.

Elucidating the endocrine and paracrine regulation of human ovarian follicular waves is important for understanding follicle-oocyte interactions, by which non-invasive markers may be identified for predicting the number and quality of oocytes obtained through the synchronization of ovarian stimulation or predicting the ovulatory potential of follicles comprising anovulatory follicular wave.

Summary and conclusions

The theory of human ovarian follicular waves has inspired the researchers and clinicians for exploratory development of ART and will have profound implications for infertility treatment and fertility preservation. The development of more than one wave of folliculogenesis during women's cycle provides the possibilities for new ART regimens. The approach which attempted to optimize outcomes of ART and urgent fertility preservation based on the theory of ovarian follicular waves, such as synchronization of follicle wave emergence by different ways in ovarian stimulation, luteal phase oocyte retrieval, have been reported. However, to a large extent, the mechanisms of primordial follicle activation and antral follicular recruitment are far from being fully understood [49]. Further prospective studies are needed to confirm the findings. With the knowledge of physiological recruitment of antral follicle waves, we may not only develop safer, more efficacious and patient-friendly ART protocols but also improve the ART outcomes for the infertile patients with normal or abnormal ovarian reserve.

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