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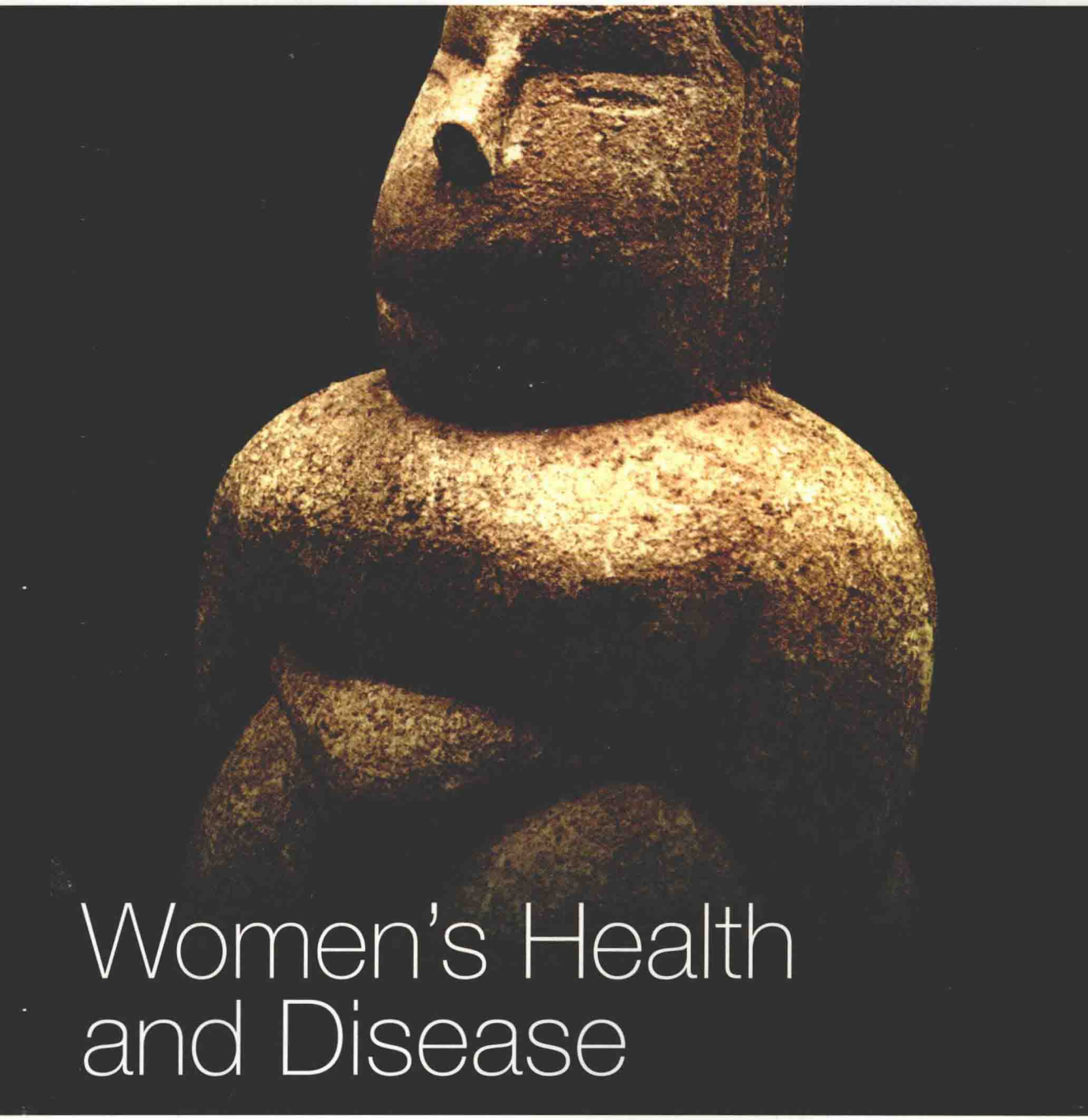

Women's Health and Disease

ISSUE EDITORS

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Continuing education and clinical research for the training of obstetricians and gynecologists in Europe

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The need for doctors to develop in their profession and in science applies to all ages and at all hierarchical levels. This development can be sustained both via education and research. In this brief paper, we examine certain crucial aspects of education and research in obstetrics and gynecology (OB/GYN) as they are actually observed in Europe. The need for uniform development of continuing professional development (CPD) among all European countries is progressively becoming apparent. There is no single approach to CPD. Junior doctors should benefit from the teaching of senior obstetricians and gynecologists, especially those in a hierarchical system of training that must assure their progress. Hospital visiting organized by EBCOG enables OB/GYN departments of teaching hospitals to unify their teaching and learning approaches. Furthermore, improving the ability of trainees and specialists to conduct clinical research is vital, as this will transform the breakthroughs of basic science into clinical practice. A formal training period in research should be available to most competent trainees in OB/GYN in addition to their basic clinical training.

Keywords: clinical research; continuing professional development; European Board and College of Obstetrics and Gynecology; obstetrics and gynecology

Introduction

Since the Hippocratic era when medicine was organized for the first time as a distinct application of humanitarian sciences with a social function, progress in this field has been founded on the responsible transmission of knowledge and skills from trainer to trainee. The need for doctors to develop in their profession and science applies to all ages and at all hierarchical levels.[1] Concurrently with this almost ritually practiced educational process, it became apparent that progress could be sustained only via development of new knowledge. Thus, research appeared as an equal partner of education regarding the everlasting goal for improvement of medicine in the service of humankind. In this brief paper, we try to examine certain crucial aspects of education and research in the discipline of obstetrics and gynecology (Ob/Gyn) in the way they are actually observed in Europe.

Never-ending education

The need for uniform development of continuing professional development (CPD) activities among all European countries within the discipline and beyond is becoming progressively apparent. The Ob/Gyn Section of the Union Européenne des Médecins Spécialistes (UEMS) is playing an important role in this respect. The CPD activities must be based on four major elements: identification of needs, objectives, effective interventions, and evaluation of the results on patient care. There is no single approach to CPD; it is rather a range of interventions such as introduction and promotion of problem-based learning in postgraduate educational activities. The most influential obstetricians and gynecologists are those working in university and district hospitals. Junior doctors should benefit from teaching of senior obstetricians and gynecologists, especially those in a hierarchical system of

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training that must assure their development and progress in science and clinical skills.[2,3] This goal seems to be effectively served by the European Board and College of Obstetrics and Gynecology (EBCOG), which in order to improve training in the discipline, developed a hospital visiting policy implemented in 1996. Visits provide an opportunity for the visited department to seek suggestions for improvement.[4] Hospital visiting enables Ob/Gyn departments of teaching hospitals to share experiences, to promote a better understanding of regional priorities and resources and, ultimately, to unify their teaching and learning approaches. However, the EBCOG hospital visiting program avoids implementation of a rigid educational approach. Peer influence is used as a tool to promote convergence toward higher standards throughout the European Union, with the aim of improving women's health care.[5] Sooner or later, EBCOG may be looking beyond Europe and seek collaborative alliances with sister societies in North America or other countries to further improve guidelines and practices for hospital visiting.

Regarding CPD, digital technology, electronic communication, and alternative effective strategies to assist the professional development of obstetricians and gynecologists (particularly those who live in rural areas) should be developed and used effectively. Others, will meticulously look for educational activities (congresses, scientific fora, specialized courses, etc.), which might provide the best for the application of evidence-based medicine.[6] The scientific societies involved in CPD have a key role to play in the future by providing opportunities for continuing education.[1] Ultimately, emphasis must be placed on quality of CPD rather than quantity.[7]

Does clinical research need revitalization?

Many countries in Europe experience a decline in clinical research that affects Ob/Gyn. Since the academia and the National Health System (NHS) hospitals require a strong clinical research background, a combined work is required by EBCOG, the European Union authorities, medical charities, and the National Ministries and Medical Councils. Over the past decades, the progress in molecular and genetic research has moved a part of researchers from bedside to laboratory bench.[8] This may have affected the availability of clinical researchers who evaluate the results of the fundamental science and "translate" the advances into new treatments (translational or "bench-to-bedside" research). Concerns also exist about the low patient recruitment rates, high costs, European and national constraints,[9] and the reduction in the noncommercial clinical trials.[10] Doctors who work in a university or teaching hospital keep up with the tripartite nature of academic medicine by carrying out teaching responsibilities, delivering the health service to the patients, and at the same time performing clinical research.[11] Inevitably, manuscripts produced by clinical researchers in these institutions are rarely published in high-impact journals as compared with those of their colleagues working in fundamental research.[12] In addition, clinical researchers in academic medicine may select the topics for their research, driven by the state of funding and publication pressures.[5] Non-academics who perform research have to keep trying hard to maintain updated critical appraisal skills in order to avoid a two-rank categorization within the specialty. Junior and postdoctoral researchers have difficulties in obtaining one of the limited fellowships; while trainees in Ob/Gyn cannot get a formal research period within their specialty should they elect to do so.

In 2004, 50 academic departments around Europe responded to a questionnaire sent by the president of the EBCOG to the heads of academic departments in Ob/Gyn. Eighty-two percent of the academic departments had major problems in attracting research grants, 10% of the remaining departments had growing problems as compared to the past, whereas only 8% answered that they had no problems. Among the problems identified were the competition with nonclinical research groups, the overwhelming bureaucracy in applying for a grant, and the difficulty in the recruitment of trainees to undertake clinical research. Fifty percent of the departments did not include a formal period for research during training, whereas in 20% of them, extra time was planned, but owing to clinical and administrative workload, this did not come into effect in most of the cases. Only 30% of the academic departments replied that a period for research is integrated in their training program, but for the majority of trainees, this was a short period (A. Van

Assche, unpublished data). Recruitment problems due to insecure funding must be effectively faced, and the trainees who wish to undertake research should be encouraged to develop relevant skills as they simultaneously carry out duties related to the care of the patient.[10,13]

Furthermore, there is a need for large clinical trials between Ob/Gyn departments. A network for clinical research will provide a way for people and ideas to merge, attract potential investments and avoid repetition of the effort across Europe and beyond. A research network may not be exclusively dedicated to clinical Ob/Gyn research, but it may be built up by multidisciplinary partnerships, including professionals with a special interest in medical education and service development. Proper infrastructure is essential before discussing funding for projects and further expansion of the clinical research in a department.[14] National or European funds are an option to support noncommercial clinical trials, while a provision for updating the skills of the clinical researchers should be an integral part of any new funding within the department. EBCOG and individual academic centers can help towards a vigorous European research environment by taking initiatives on every part of the circle, that is to organize researcher workshops, produce policy documents or provide information about research grants.[15]

Conclusions

The need for uniform development of CPD activities among all European countries within the discipline and beyond is becoming progressively apparent. There is no single approach to CPD. Junior doctors should benefit from the teaching of senior obstetricians and gynecologists, especially those in a hierarchical system of training that must assure their development and progress in science and clinical skills. Hospital visiting organized by EBCOG enables Ob/Gyn departments of teaching hospitals to share experiences, to promote a better understanding of regional priorities and resources and, ultimately, to unify their teaching and learning approaches. As the practice of Ob/Gyn evolves locally and internationally, a more central planning of the CPD activities is required by the respective societies in Europe. Finally the design of an effective CPD program should account to the patients, the health care purchasers, and the doctors.

Furthermore, improving the ability of trainees and specialists to conduct clinical research is vital, as this will transform the breakthroughs of basic science into clinical practice. Further mobility of the clinical researchers in Europe must be supported as it is expected to assure a greater development between national and continental projects. Appropriate attempts can also get new investments from industry and pharmaceutical companies provided they could see new prospects. Provided that university departments engage in such programs, an increasing number of doctors will be taught to produce high-quality noncommercial clinical trials that also fulfill all legal responsibilities. A formal training period in research should be available to most competent trainees in Ob/Gyn in addition to their basic clinical training.

Conflicts of interest

The authors declare no conflicts of interest.

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The role of gonadotropins in the follicular phase

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Folliculogenesis in humans is a lengthy process that involves several regulators. Pituitary gonadotropins play crucial roles in the late stages, particularly in the last 15 days of follicle maturation. During the intercycle rise of follicle-stimulating hormone (FSH), selection of the dominant follicle takes place. This is a complex process that also involves locally produced substances. At the same time, luteinizing hormone (LH) stimulates the synthesis of androgens, which serve as the substrate for the production of estrogens. During the second half of the follicular phase, the follicle becomes dependent on LH. Induction of multiple follicular development by exogenous FSH results in a marked suppression of endogenous LH. For normal follicle maturation, both an LH threshold and an LH ceiling have been considered. In the context of an *in vitro* fertilization program, application of protocols for ovarian stimulation that will prevent the marked suppression of endogenous LH secretion might provide a better approach to treatment optimization.

Keywords: FSH; LH; follicle; follicular phase

Introduction

The human premenopausal ovary contains follicles at different stages of development, from the primordial to the preovulatory size. Following ovulation, the corpus luteum is formed from the remnants of the ruptured follicle. On the basis of their size and on the number of granulosa cells, we classified human follicles into eight classes, with class 1 corresponding to the preantral secondary mature follicle and class 8 to the large preovulatory follicle.[1] Human folliculogenesis is a lengthy process.[2] A primordial follicle needs approximately 1 year to become preovulatory.[1] The factors that are responsible for the maturation of the follicles are not the same throughout the different stages. There are, however, differences between animals and humans regarding the triggering mechanisms of follicle maturation, particularly at the early stages.

Initial recruitment

Initiation of maturation of the follicles from the primordial pool is a process that at least in humans is not dependent on gonadotropins. Although follicle-stimulating hormone (FSH) is a primary factor controlling folliculogenesis, the "initial recruitment" of human primordial follicles is mainly controlled by factors produced in the ovaries. Nevertheless, in animals, gonadotropins appear to play a crucial role even at these early stages of folliculogenesis.[3] Among the local factors produced by the granulosa and/or theca cells, insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), transforming growth factor-α (TGF-α), and TGF-β play important roles. At the early stages, the antimullerian hormone (AMH) is also important both in animals and humans.[4,5]

Substances produced by the oocyte, such as growth differentiation factor-9 (GDF-9) and bone morphogenetic protein-15 (BMP-15) also participate in the control of follicle maturation.[6] They play a role in the differentiation into different subgroups of the granulosa cells that surround the oocyte.[7] These factors stimulate the proliferation of the granulosa cells and contribute to the prevention of premature luteinization.[7] Although initial recruitment and the passage of a follicle from the preantral to the antral stage in humans is FSH independent, the

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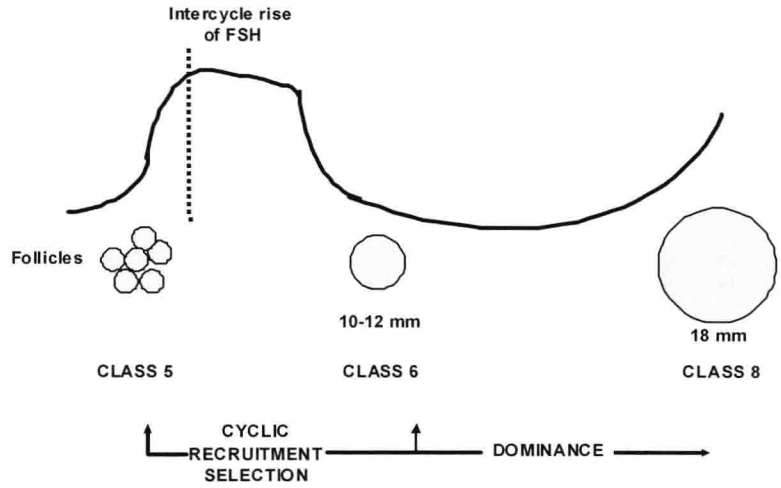

Figure 1. FSH intercycle rise during the luteal–follicular transition leading to the selection of the dominant follicle. The selected follicle grows further despite the declining concentrations of FSH.

development of the follicles from class 1 to class 5 is to some extent affected by the tonic secretion of gonadotropins.[1] It has been estimated that a follicle needs approximately 85 days to mature from class 1 to class 8.[1] The last 15 days of follicle maturation in humans correspond to the follicular phase of the menstrual cycle and are entirely dependent on the action of the two gonadotropins. This means that below a certain threshold of FSH and luteinizing hormone (LH) levels, follicle maturation to the preovulatory stage will not take place with consequent menstrual irregularities.

Growth of antral follicles

Cyclic recruitment

The two gonadotropins play distinct roles in follicle maturation. The intercycle rise of FSH, also called "FSH window," that takes place during the luteal–follicular transition[8,9] is responsible for the so-called "cyclic recruitment" and the selection of the dominant follicle (Fig. 1).[10] The amount of FSH that is required for follicle stimulation has not been defined, although an intercycle increase of at least 30% over the basal value has been considered a threshold level.[11] During the process of follicle recruitment, FSH is accumulated in the follicular fluid and stimulates the production of steroids from the granulosa cells.[12]

It is not only FSH, but it is also LH that is important at this stage of folliculogenesis. In particular, the two gonadotropins collaborate in the context of the two-cell two-gonadotropin theory with LH acting on the theca cells to stimulate the production of androgens, which then are transferred into the granulosa cells to be aromatized into estrogens under the influence of FSH.[13] The enzyme that is responsible for this process is P450 aromatase and is produced under the influence of FSH.[14]

Growth factors

The effect of the two gonadotropins on follicle maturation is influenced by the autocrine and paracrine actions of substances produced locally in the ovaries. Such substances include the system of inhibins and activins, the IGFs and their binding proteins (IGFBPs), androgens, and estrogens. Especially, in the early follicular phase, inhibin produced by the granulosa cells enhances the action of LH on the theca cells for the production of androgens, whereas activin antagonizes this action but at the same time augments the effect of FSH on the aromatization of androgens into estrogens.[15] Under these conditions, activin facilitates the estrogenization of the follicular environment, a process that is very important for the survival of the follicle.

The IGFs are usually bound to IGFBPs, becoming thus inactive. With the action of FSH on the granulosa cells, a protease, similar to pregnancy-associated plasma protein-A (PAPP-A), is produced that degrades IGFBPs, and therefore IGFs become free and available for action.[16] The two IGFs, IGF-1 and IGF-2, are expressed in the granulosa cells of

various species and are detectable in the follicular fluid. These factors stimulate proliferation of the granulosa cells and the production of estrogens by sensitizing the follicle to the two gonadotropins.[17]

The follicle with an adequate amount of FSH in the follicular fluid and an optimal number of FSH receptors in the granulosa cells is rescued and has the potential to grow further. In contrast, follicles with low FSH concentrations have an androgenic environment and become atretic. Aresia is an apoptotic process that is enhanced by the androgens.[18] However, androgens in low amounts may sensitize the granulosa cells to FSH and therefore facilitate the growth of the follicle.[19] Estrogens may also participate in follicle growth by increasing the sensitivity of the follicle to FSH.[20] Whether folliculogenesis is also affected by substances derived from extragonadal sites, such as leptin and ghrelin, has not been clarified.[21,22]

Growth of the dominant follicle-LH dependence

The selected FSH-dominant follicle produces and releases in the circulation estradiol more quickly than the other follicles. The increasing concentrations of this steroid in blood suppress FSH levels via a negative feedback effect leading to single follicle selection.[23] The dominant follicle can grow further and the growth rate estimated by ultrasound is almost linear.[24] This happens despite the declining concentrations of FSH and is due first to the action of various intra-follicular regulators and second to the fact that the follicle becomes gradually dependent on LH (Fig. 1).

Intra-follicular substances produced by the oocyte, the granulosa cells, and the theca cells sensitize the granulosa cells to the decreasing concentrations of FSH.[2] At this stage, the action of inhibin on LH-stimulated production of androgens in the theca cells is more pronounced than in earlier stages, whereas activin enhances the action of FSH on the aromatization of androgens into estrogens.[15] Also, BMP-4 and BMP-7, produced from the theca cells under the influence of LH, are important. These proteins on one hand stimulate the production of aromatase and on the other hand inhibit FSH-induced steroidogenic acute regulatory protein (STAR), which is important for the production of progesterone.[25] This is at least part of the mechanism via which LH prevents premature luteinization during the follicular phase of the cycle.

During the second half of the follicular phase, the follicle becomes dependent on LH as LH receptors appear on the granulosa cells under the influence of FSH.[26] Therefore, LH can directly stimulate the production of estrogens and the proliferation of the granulosa cells.[27] The dependence of the selected follicle on LH is a gradual process, that is, the follicle gradually becomes less dependent on FSH and more on LH.[28] The growth of the follicle may also be affected by actions exerted between neighbor cells and follicles via the production of the granulosa cell inhibitory factor, although this has not been fully clarified.[29] As the follicle grows, the granulosa cells differentiate morphologically and functionally into three main layers.[7] Those nearer the oocyte are the cumulus cells with a high mitotic index and continuous proliferation, while those in the outer layer, called membrane of mural cells, express LH receptors and steroidogenic enzymes. In between the two layers there are the intermediate or periantral cells.

LH threshold

Although LH is required both for steroidogenesis and the growth of the dominant follicle, the least amount of this hormone required is difficult to define. Treatment of normal women during the late follicular phase of the cycle with a single dose of 3 mg of the GnRH antagonist, cetrorelix, resulted in a decline in serum estradiol, LH, and FSH concentrations and in follicle growth arrest.[30] Following elimination of the activity of the antagonist, LH and FSH levels increased again and follicle growth resumed.[30] When a GnRH antagonist was given to normal women in the midfollicular phase in combination with FSH injections, follicular growth arrest was prevented and the growth rate was similar to that of the dominant follicle in untreated normal menstrual cycles (Fig. 2). Although these data demonstrate the role of FSH, LH is also important. In fact, when a follicle was recruited by the administration of exogenous FSH, given up to the time the follicle reached the size of 14 mm in down-regulated cycles, the growth of the follicle was sustained with the administration of LH alone, suggesting a role for this hormone in the final stages of follicular maturation.[31]

One would argue if LH alone can stimulate the growth of a follicle before the action of FSH, i.e., at

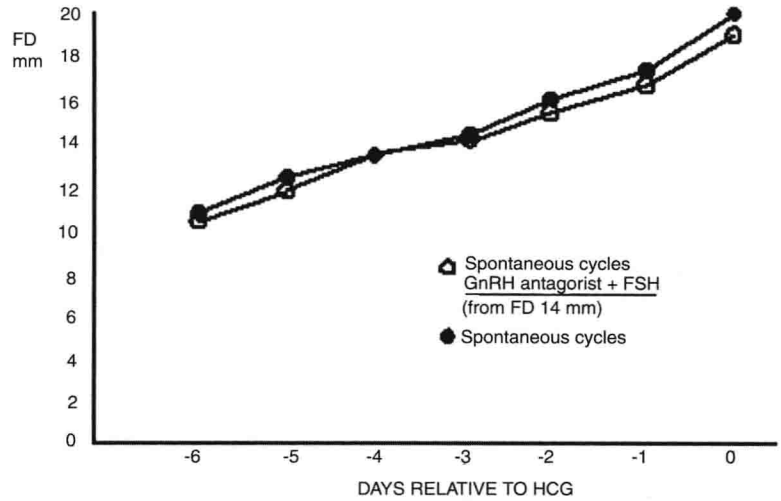

Figure 2. Mean follicle diameter calculated by ultrasound scans of the ovaries in spontaneous cycles of 50 women undergoing intrauterine insemination. Day 0 is the day of the administration of HCG. The diagram is based on unpublished data (Messinis I.E., Papastergiopoulou L., and Dafopoulos K.).

the early stages of "cyclic recruitment." Information has been derived from experiments performed in down-regulated cycles in which however very little benefit was found by the pretreatment with LH.[32] In the extreme condition of hypogonadotropic–hypogonadic women, who lack endogenous LH, the exogenous administration of FSH alone was able to stimulate the growth of follicles up to the preovulatory size, but serum estradiol concentrations were extremely low.[33] When in such patients both FSH and LH were given, estradiol concentrations increased markedly suggesting that LH is required for the production of the steroids.[34] This suggests that FSH is the principal hormone needed in clinical terms for ovarian stimulation. Although FSH can stimulate the growth of follicles without the presence of LH, LH receptors seem to play a permissive role for the action of FSH.[35]

Multiple follicular development

In IVF cycles treated with the exogenous administration of FSH, the FSH window is widened leading to the selection of multiple follicles. As a result, the negative feedback effect is potentiated due to the overproduction of estradiol and inhibin.[36] Consequently, the secretion of LH and FSH from the pituitary is markedly suppressed as it has been shown in several studies. In one study, when exogenous FSH, urinary, or recombinant, was given to normal women for induction of multiple follicular development in non-down-regulated cycles, LH was significantly reduced within 24 h from the onset of treatment and the LH levels remained low throughout the whole period of stimulation.[37]

Endogenous LH is also suppressed during ovarian stimulation in down-regulated cycles after the use of a GnRH agonist and also in cycles in which a GnRH antagonist is injected.[38] The secretion of LH is not suppressed when clomiphene citrate or a GnRH agonist in a short protocol are used in combination with FSH.[39,40] In cycles in which LH is suppressed, it is difficult to define a specific threshold of this hormone for follicle growth, production of steroids, and oocyte maturation. When the level of 0.5 IU/L was taken as a cut-off point, the results were contradictory. The conclusion based on a meta-analysis was that one could not predict the outcome of treatment in IVF cycles on the basis of serum LH concentrations.[41] In the literature, there has been debate as to whether exogenous LH should be added to the FSH regimens to compensate for the marked suppression of endogenous LH secretion.[42]

The suppression of pituitary LH secretion is also evident at midcycle in FSH treated cycles. In such cycles, the endogenous LH surge is either blocked or markedly attenuated because of the overproduction of the gonadotropin surge attenuating factor (GnSAF).[36,39] When a GnRH antagonist is used, premature LH peaks occur on several occasions due

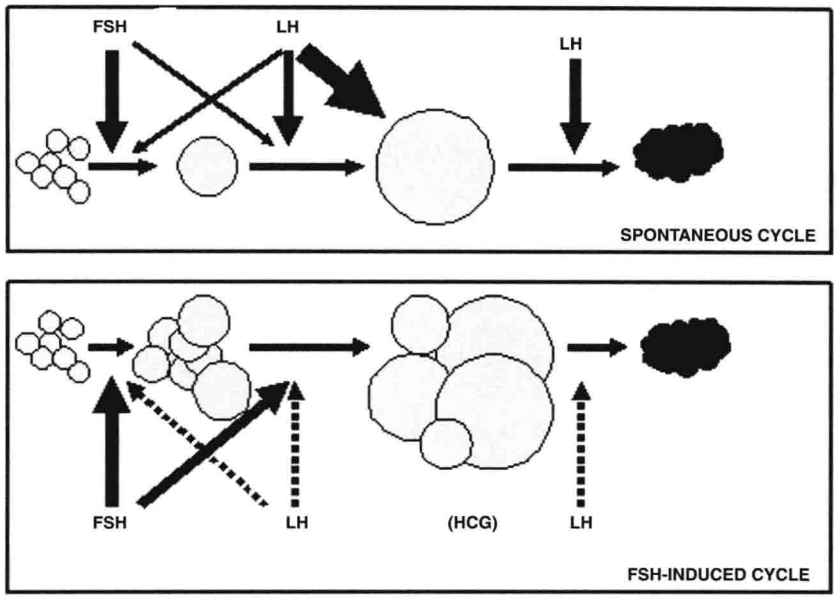

Figure 3. Differences related to the actions of the two gonadotropins and the number of the selected follicles between untreated spontaneous cycles and cycles induced by the exogenous administration of FSH. In the untreated cycles FSH acts mainly in the first half, while in the FSH-induced cycles throughout the whole follicular phase. On the other hand, LH predominates in the second half of the follicular phase and at mid-cycle of the untreated cycles, while its secretion is markedly reduced in the FSH-induced cycles. Multiple follicles develop during treatment with FSH.

to the inability of these drugs to block the positive feedback effect of estradiol.[43,44] It is likely that the action of GnSAF facilitates the action of the GnRH antagonist, converting thus a premature LH surge into an abortive surge.

LH ceiling concept

Apart from the LH threshold, an LH ceiling concept has been also proposed for normal follicle maturation and steroidogenesis.[45] Under normal conditions, the levels of LH during the follicular phase remain low and increase markedly only at midcycle, when the positive feedback effect of estradiol leads to the occurrence of the endogenous LH surge. The huge amount of LH secreted during the LH surge is responsible for marked changes in the follicle including the induction of genes in the granulosa cells that are important for luteinization and the production of progesterone.[46] This, however, is a normal process, but if it happens before full follicle maturation, it will result in premature luteinization, which will jeopardize the maturation of the follicle and the oocyte.[25] An increase in LH concentrations by the exogenous administration of LH during the application of different ovulation induction protocols might be beneficial because smaller follicles will become atretic and, therefore, only a cohort of large or even a single follicle will become preovulatory.[47] Nevertheless, the LH ceiling is difficult to define, although preliminary data are encouraging.[47]

Conclusions

There are differences between spontaneous and FSH-induced cycles in women (Fig. 3). In a spontaneous normal cycle, the two gonadotropins play important roles in follicle growth, production of the steroids, and maturation of the oocyte. In FSH superovulated cycles, FSH is given throughout the whole follicular phase and this results in follicle growth, but the production of LH is markedly reduced. It is evident that in such cycles the secretion of LH can be sufficient for steroidogenesis and normal follicle maturation via a balanced approach related to drugs dosages and protocols selection.

Conflicts of interest

The authors declare no conflict of interest.