Reproductive Toxicity of Ovulation Induction

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ABSTRACT—*The development of ovulation-inducing drugs has enabled clinicians to more effectively treat the hypothalamic, pituitary, and ovarian abnormalities resulting in infertility. Pregnancy rates have been improved with the use of agents such as clomiphene citrate (CC), human menopausal gonadotropin [hMG or follicle-stimulating hormone (FSH) preparations], with gonadotropin-releasing hormone (GnRH) and its analogs, stimulating the development of multiple ovarian follicles and increasing the number of fertilizable oocytes. The use of these drugs is not without certain detrimental or "toxic" consequences. The negative effects from superovulation can occur during follicle development, decreasing the number of healthy oocytes and embryos capable of leading to viable pregnancy. Ovulation induction can lead not only to higher incidences of spontaneous abortions, and multiple and ectopic pregnancies, but also to poor pregnancy rates, due, in part, to asynchrony between embryonic development and the uterine environment. Diseases such as ovarian hyperstimulation syndrome (OHSS), resulting in the secretion of supraphysiologic levels of estradiol, can lead to severe health complications, possibly requiring hospitalization. Most drugs used for ovulation induction can lead to OHSS. Although incidences of OHSS following CC use are less frequent, CC has been associated with hot flushes, multiple gestations, visual disturbances, cervical mucus abnormalities, and luteal phase deficiency. Finally, there are reports that link any or all of the ovulation-inducing drugs with a higher incidence of ovarian and breast cancer, however, a cause–effect relationship has yet to be proven.*

KEY WORDS: gonadotrophins, ovulation induction, toxicity, fertilization

INTRODUCTION

The previous decade has seen the rapid development of assisted reproductive techniques utilizing a variety of ovulation-inducing agents for anovulatory women, as well as for women undergoing assisted reproductive technology [ART: in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT)]. The development of ovulation-inducing drugs have enabled clinicians to more effectively treat the hypothalamic, pituitary, and ovarian abnormalities resulting in infertility. The indications for the use of these agents have broadened as more information has become available about them, resulting in a more widespread clinical use.

The first pregnancy established using IVF actually occurred as the result of an unstimulated cycle, and the oocyte retrieval was coordinated with the preovulatory surge of luteinizing hormone (LH). Reports regarding the efficacy of unstimulated cycles have concluded that, although less expensive, the delivery rate from these cycles was extremely low (~ 6%), making this a very impractical means of achieving pregnancy.[1] Pregnancy rates were improved with the use of ovulation-inducing drugs such as clomiphene citrate (CC), human menopausal

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gonadotropins (hMG or FSH preparations) and gonadotropin-releasing hormone (GnRH) and its analogs, which stimulated the development of multiple ovarian follicles, facilitating the recovery of greater numbers of fertilizable oocytes.[2]

The process of superovulation or controlled ovarian hyperstimulation (COH) has become widely used in humans as a means of increasing the number of embryos per patient. The procedure, however, is not without certain detrimental or "toxic" consequences. Each drug is associated with its own specific adverse effects, and although many of them are benign and self-limited, some of the side effects of infertility drugs, particularly the exogenous gonadotropins, can be quite serious, if not life threatening.[2]

The negative repercussions from superovulation can occur throughout the various stages of follicle development and oocyte maturation, decreasing the number of healthy embryos capable of leading to a viable pregnancy. Moreover, prolonged exposure to exogenous gonadotropins will stimulate excessive steroid production by the ovaries, resulting in reduced pregnancy rates due to asynchrony between embryonic development and the uterine environment.[3] Still other reports correlate the use of ovulation-inducing drugs with a higher incidence of both multifetal gestations[4,5] and ectopic pregnancies.[6] The purpose of this article is to provide an overview regarding the relative toxicity of ovulation induction on subsequent reproductive response, as well as on the general health of anovulatory or otherwise infertile women.

PHYSIOLOGY OF OVULATION

General Overview

Before we consider the effects of superovulation on reproductive processes, detrimental or otherwise, it is important, for comparison purposes, to review the events that lead to ovulation during an unstimulated cycle.

Role of Gonadotropins in Follicle Growth

The ovary is a dynamic and complex organ. It is responsible for the cyclic production and release of mature oocytes, the subsequent formation of functional corpora lutea (CL), and the maintenance of the proper balance of steroid hormones and pituitary gonadotropins. The regulation and control of oocyte function are complex processes involving both local (paracrine, such as steroids) and extraovarian (endocrine) factors. The principle endocrine hormones modulating oocyte development are, in part, the pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH is considered to be primarily responsible for follicle growth and oocyte development in most species, including humans. LH is responsible mainly for maturing the follicle and oocyte just prior to ovulation, but when present in prematurely elevated levels can, in fact, be toxic to oocyte development.[7,8]

It is still unknown why individual follicles are selected to enter the growing population, while apparently identical neighboring follicles remain unaffected. Only a very small percentage of follicles ovulate (less than 1% in women). It well known that mammalian oocytes are arrested in prophase I of meiosis at or before birth. Of the several million oocytes present at this time, only a few hundred are destined for ovulation during a normal reproductive life span, with the vast majority lost through atresia. Evidence for the involvement of the pituitary in maintaining early follicle growth is presented in a study using the hypophysectomized rat as a gonadotropin-deprived model. These investigators observed that hyophysectomy did not prevent growth of small follicles (two layers of granulosa cells) to the four-layer stage.[7] When compared to comparable follicles from pituitary-intact animals, a higher number of antral follicles, however, failed to continue to develop and became atretic. Hypophysectomy also resulted in a reduction of size and number of slightly larger follicles within 20 days following surgery. These follicles were unable to develop past the three-layer stage and degenerated.[9] Lack of gonadotropin stimulation is vital to normal follicular development, and even simply altering gonadotropin release at any time during the follicular phase can lead to premature luteinization or atresia.[10]

Effect of Gonadotropins on the Oocyte

To date, no reports exists in the literature describing gonadotropin receptors on the oocyte itself. The actions of LH and FSH on oocytes are presumably indirect, stimulating the synthesis and secretion of paracrine mediators from the follicle cells, the granulosa and theca. Under gonadotropic stimulation, these cells function both separately and together to synthesize the necessary steroids, growth factors, cytokines, oocyte maturation inhibitor, inhibins and activins required for normal follicle and oocyte development.[10,11,12] Optimal function of follicle cells depends on another means of cell-cell communication, specialized junctional elements called gap junctions. These channels allow syncycial communication to occur between mural granulosa cells (those lining the follicle) and the cells of the cumulus which surround the oocyte. Both gonadotropins may influence oocyte development by modulating the direct communication (formation of gap junctions) and

transfer of mediators from the granulosa cells to the oocyte.[8]

Role of Gonadotropins in E_2 Biosynthesis

Using the rat model, pioneering work by Greep in 1949[13] and Falk in 1952[14] demonstrated that optimal E_2 secretion by the ovary required the cooperation of the theca and granulosa cells, following the appropriate gonadotropic stimulation. Based on studies in many species, including humans, the "Two-Cell/Two-Gonadotropin Theory" of E_2 biosynthesis was developed. Briefly, this hypothesis states that following stimulation by LH, theca cells synthesize and secrete androgens, which are then aromatized to estrogens under the influence of FSH.[15,16] The steroid hormones, especially E_2, can modulate follicle growth either locally, directing mitotic cell growth and inducing the synthesis of their own receptors, or peripherally, via regulation of gonadotropin synthesis and secretion.[17]

RATIONALE BEHIND OVULATION INDUCTION BY SUPEROVULATION

Superovulation is a process historically associated with laboratory and livestock species as a means for enhancing the availability of larger numbers of mature oocytes that would result in a higher number of offspring. The same concept applies to ovulation induction in humans. Early attempts at using natural cycles for IVF have resulted in low success rates due to the low number of oocytes obtained (generally one or two). It is logical, therefore, to assume that a regimen that stimulated multiple follicle development, resulting in an increase in the number of embryos from an individual, would substantially improve pregnancy rates. The mammalian ovary contains more oocytes than are destined to ovulate, the majority being lost to atresia.[18,19] Ovulation induction protocols "rescue" these otherwise doomed oocytes, thereby maximizing the pool of available oocytes for the specific ART procedure through a perturbation of the existing hormonal feedback mechanisms. Superovulation drugs function by reducing or removing the negative feedback influences of the ovaries on gonadotropin secretion, while enhancing the levels of endogenous gonadotropins with exogenous hormone administration.[19,20]

DETRIMENTAL EFFECTS OF OVULATION INDUCTION

General Effects of Common Stimulation Regimens

Clomiphene Citrate

In anovulatory women, generally the first line of therapy involves the use of the antiestrogen clomiphene citrate (CC). In humans, it is well documented that CC, by blocking the biological actions of E_2, results in enhanced gonadotropin secretion and maturation of more than one preovulatory follicle.[21,22,23] A recent review of the literature on ovulation induction (1992) suggested that CC still remains the drug of choice for normoestrogenic anovulation, but also indicated that if patients fail to ovulate or to conceive within six ovulatory cycles with CC, menotropin therapy is the next logical step.[22] Clomiphene can be used either alone or in combination with gonadotropins, generally hMG. Although no difference in the quality of oocytes has been demonstrated in patients treated with either CC or hMG,[24,25] several investigators have reported that the addition of hMG to CC resulted in better pregnancy outcomes for patients undergoing ART.[26] This is due, in part, to the increased numbers of oocytes achieved with the additional gonadotropin therapy,[27] and in part to improved implantation rate.[28] In any case, gonadotropins have been shown to be particularly more effective than CC in women over 35 years of age.[29] Generally, the problems associated with superovulation, such as OHSS, do not occur as frequently with CC treatment. Clomiphene has, however, been associated with hot flushes, multiple gestations, visual disturbances, cervical mucus abnormalities, and luteal-phase deficiencies (see review[2]).

Exogenous Gonadotropins and Gonadotropin-Releasing Hormone

Observations in monkeys showed that follicular development can be stimulated by either interfering with the feedback effect of estrogen or by the direct administration of exogenous gonadotropins. These results support the hypothesis that the failure of follicles to develop beyond the early antral stages during the luteal phase is due largely to gonadotropin insufficiency.[23] Although the use of gonadotropins has singularly improved oocyte yield, when used in the absence of the pituitary down regulation achieved by GnRH analogs, careful monitoring is vital to minimize cycle cancellation due to spontaneous LH surges. Protocols suppressing endogenous hormone production and release using GnRH will have the benefit of inhibiting the spontaneous LH surge, but more importantly, when combined with exogenous gonadotropins, result in an overall improvement in pregnancy rates. Both FSH and hMG have been used effectively, in this situation, for inducing follicular growth and maturation,[30] but several reports have indicated that high levels of these hormones, especially hMG, which has high intrinsic LH activity, are associated with lower pregnancy rates in IVF-ET cycles, occurring independent of other confounding factors such as, age, day 3 FSH

gonadotropins (hMG or FSH preparations) and gonadotropin-releasing hormone (GnRH) and its analogs, which stimulated the development of multiple ovarian follicles, facilitating the recovery of greater numbers of fertilizable oocytes.[2]

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levels, maximal E_2 levels, or of the number of oocytes transferred.[3,31,32,33,34,35,36,37]

DETRIMENTAL EFFECTS OF ELEVATED LUTEINIZING HORMONE

Endogenous Luteinizing Hormone

In studies of superovulation responses prior to IVF, it was noted that inappropriately elevated serum levels of LH during follicular stimulation were associated with low rates of fertilization or ongoing pregnancy.[35,38] In women undergoing IVF, a reduced fertilization rate was noted for oocytes from those patients with raised basal blood LH levels during the follicular phase of their menstrual cycles (see review[5]). The high serum LH is common in women with polycystic ovarian syndrome (PCO). The adverse effects associated with this characteristic of PCO has been described by Homberg and coworkers.[39] They found that women with PCO who were undergoing ovulation induction, using pulsatile GnRH, displayed LH hypersecretion during the midfollicular phase of ovulatory cycles. This resulted in a lower pregnancy rate or a greater risk of early miscarriage when compared to non-PCO patients undergoing ovulation induction, in whom LH levels remained within the normal range. A similar report stated that in non-PCO cases, only $\frac{1}{12}$ (8%) of cycles ended in a successful pregnancy when follicular-phase LH was elevated, compared with 54% success with cycles exhibiting normal LH.[5]

Exogenous Luteinizing Hormone

The reason for administering exogenous LH in gonadotropin-deficient women is due primarily to its role in E_2 biosynthesis of providing an aromatizable androgen substrate. It appears, however, that due to the high steroidogenic effect of LH, only minimal levels of LH are required for sufficient ovarian E_2 production. In vitro studies of LH action on human granulosa cells demonstrated that with a low dose, steroid (androgen) synthesis was enhanced without affecting cell proliferation.[40] Studies in the rat, however, demonstrated that high doses of LH suppressed aromatase activity and inhibited cell growth. Furthermore, elevated LH concentrations enhanced the synthesis of progesterone (P^4), which inhibits granulosa cell proliferation, while modulating their luteinization and creating a toxic environment for oocyte maturation.[36,41] Conception rates in vivo were also significantly reduced when LH levels were high, and the resulting pregnancies were also more likely to end in miscarriage.[39,42] Oocytes obtained from women with high serum LH during the latter stages of follicular development and just prior to oocyte retrieval were of poor quality, characterized by low fertilization and subsequent cleavage rates.[38,43] The reason for this is not completely understood. It has been postulated that elevated LH, by inhibiting aromatase activity, can result in altered androgen metabolism, leading to higher intrafollicular testosterone levels, which may impair oocyte development and contribute to the onset of follicular atresia.[11,18] Pregnancy rates were also notably lower, even if LH was elevated as late as 48 hours before hCG administration.[43]

A meta-analysis evaluating the use of FSH versus hMG showed that FSH performed significantly better than hMG and was associated with at least 50% higher clinical pregnancy rates.[44,45] Another analysis of FSH versus LH (hMG) demonstrated that fertilization and clinical pregnancy rates were higher overall for patients treated with FSH.[34] When monkeys were down-regulated with GnRH so that circulating LH levels were identical to those from hypophysectomized animals, follicle maturation and E_2 production could be induced with pure [recombinant (rec)] FSH. When the responses of these animals were compared to a similar group of monkeys treated with a combination of rec FSH + rec LH (1:1), a greater percentage of mature oocytes [meiosis II; (MII)] were recovered following treatment with rec FSH only.[33]

Interestingly, pharmacodynamic studies of FSH and hMG showed that administration of FSH was associated with a decrease in serum LH levels within the first few hours after injection.[46] In contrast, hMG injection was associated with a significant increase in circulating LH, 4 hours later. These data suggest that the beneficial effects of exogenous FSH may be mediated, in part, by its effect on blood LH levels. It would appear, then, that not only is additional exogenous LH unnecessary for follicle development, but also that it may, in fact, be detrimental for cycle outcome.

OVULATION INDUCTION AND ENDOMETRIAL RECEPTIVITY

Although LH hypersecretion has been directly associated with poor outcome in conception cycles because of poor fertilization and pregnancy rates, and increases in spontaneous abortions, its negative mechanism of action may, in fact, be indirect. Its detrimental effects on the oocyte, such as premature resumption of meiosis, can be attributed to its effects on the mural granulosa and cumulus cells. Similarly, the reported adverse actions of LH on the uterine environment may most likely be indirect, achieved through ovarian intermediates such as steroid hor-

mones, growth factors, inhibins and activins, which act directly on the endometrium.[3,9,20]

Normally, the secretion of steroid hormones by the ovary during an ovulatory cycle and early pregnancy ensures that uterine preparation for implantation coincides with the presence of a mature blastocyst. Prevailing evidence suggests that appropriate concentrations of both E_2 and P_4 are essential for successful implantation of the developing embryo.[47] For most mammalian species, E_2 stimulates the mitotic proliferation of the endometrium, along with an increase in vascularity. Progesterone, secreted during the luteal phase, inhibits further mitotic activity and induces glandular secretion.[3,19] Optimal conditions for embryo implantation, therefore, depend on carefully orchestrated actions and interactions of factors on the endometrium. Evidence from studies using laboratory rodents, and from humans, has suggested that an imbalance in the relationship of these factors can lead to pre- or postimplantation embryonic death.[48,49]

However, the relative importance of the synchronous development of the endometrium versus embryo quality on implantation after ART is still somewhat controversial. One study of patients under 35 years of age, undergoing ART, compared pregnancy and implantation rates achieved during routine stimulated cycles (menotropins) and in hormone replacement cycles (E_2 and P_4) using donor oocytes. These results showed that no significant differences in uterine receptivity were noted between the two groups.[50] Other evidence suggests that ovarian hyperstimulation can be deleterious to uterine receptivity. A later study revealed that higher dosages of gonadotropins (5 vs. 3 ampules hMG/day) administered to patients undergoing pituitary down regulation were associated with poor pregnancy outcomes, regardless of age, basal FSH levels, endometrial thickness, maximal E_2 levels, number of oocytes retrieved, and number of good quality embryos transferred.[32,51] Since no other differences could be established, these authors concluded that the deleterious effect of the higher dose of hMG on pregnancy outcome was on the endometrium.

Endometrial morphology, steroid hormone receptors, and serum steroid concentrations in 22 infertile women were examined. Following treatment with a combination of GnRH/hMG/hCG, there was a significant reduction in the number of nuclear E_2 and P_4 receptors in both the glands and stroma. Surprisingly, these endometria still appeared "in phase" morphologically with serum hormone levels. The authors concluded that a reduction in endometrial steroid receptors occurs after ovulation induction in the presence of supraphysiological steroid levels, but is not associated with alterations in endometrial microanatomy.[52] Salat-Baroux and coworkers[53] compared endometrial E_2 receptor levels in patients during a natural ovulatory cycle. However, when compared to those measured during an ovulation-induction cycle using GnRHa/hMG, no differences in receptor concentrations between the two groups were found.[53] In spite of these data, other investigators still believe that abnormally high E_2 may act to advance the age of the endometrium, narrowing the window for implantation.[8]

PREGNANCY COMPLICATIONS FOLLOWING OVULATION INDUCTION

Pregnancies resulting from ART and ovulation induction are more associated with increased incidences of complications than those occurring spontaneously. There are higher reported rates of ectopic, heterotopic, and multifetal pregnancies, spontaneous abortions, and premature deliveries.[54]

Ectopic Pregnancies

The association with ovarian hyperstimulation suggests that endocrine factors (possibly high E_2) may contribute to the increased rate of ectopic pregnancy. Fernandez and coworkers[55] also demonstrated that ovulation induction for insemination was positively correlated with an increased risk of ectopic pregnancy, but that ovulation induction for IVF did not pose a further increase in risk. In another study, 289 anovulatory women with apparently normal fallopian tubes were treated with hMG. There was a 2.7% overall ectopic pregnancy rate for the resulting 379 conceptions, which was a threefold increase over the general population.[56] A study of 380 ART procedures retrospectively demonstrated a 2.24% incidence of ectopic pregnancies for this population as a whole. When analyzed in terms of drugs used, there was a higher incidence of ectopics reported for patients treated with CC + hMG (7.8%) than with GnRH + hMG (2.18%). These percentages did not appear to be due to an increase in the number of embryos replaced, nor was embryo placement involved (ie, intrauterine vs. intrafallopian tube),[6] suggesting that possibly hormonal (nonphysical) factors may be involved in the development of ectopic pregnancy.

Multifetal Pregnancies

In vitro fertilization and related techniques have contributed to the increasing rate of multiple gestations.[57] The incidence of multifetal pregnancies rose from 16% to 39% in the early 1960s with the introduc-

tion and use of ovulation-inducing drugs.[58] There is still debate over the optimal number of embryos transferred, and most clinicians will agree that there is a strong patient effect as to how many embryos will result in a normal, singleton pregnancy. Although implantation and pregnancy rate improve as the number of embryos or oocytes transferred during IVF or GIFT procedures increases, so does the rate of multifetal pregnancies.[4] Depending on the patient's general health and the number of fetuses present, the complications associated with multifetal gestations are numerous and can be quite serious, such as increases in prematurity, perinatal morbidity, and mortality. Patients with multifetal pregnancies are more likely to choose fetal reduction, which can result in up to 30% loss of the entire pregnancy.[4,58] In another study, 82 CC-resistant, anovulatory patients were treated with the combination of GnRH and exogenous gonadotropins, according to a "step-down" regimen in which initial gonadotropin doses were 1.5–2.5 ampules/day and then decreased to .5/day. Although ovulation and pregnancy rates were not different in these patients compared with those undergoing the more routine "step-up" protocol, there was, however, a lower incidence of complications, specifically multiple gestations associated with the low-gonadotropin "step-down" regimen.[60]

OVARIAN HYPERSTIMULATION SYNDROME

One complication most closely affiliated with use of ovulation-inducing agents is OHSS.[61,62] OHSS is an iatrogenic condition manifesting itself in a wide spectrum of clinical and laboratory characteristics, with an incidence of .1%–4%. Ovulation induction is usually followed by OHSS, and all drugs used for this purpose (CC, FSH, hMG, GnRHa) are capable of inducing this syndrome in varying degrees.

A comparative study of patients with clinical and biological characteristics of OHSS showed that these individuals were younger, with fewer incidences of tubal pathology. OHSS patients exhibited ovarian hypersensitivity, reflected by extremely high E_2 peak levels in response to lower doses of hMG. Interestingly, these patients have a greater chance of becoming pregnant, probably due to the collection of a greater numbers of fertilizable oocytes.[63]

Several complications accompany OHSS, some of which can be life threatening. OHSS is generally characterized by ovarian enlargement and increased capillary permeability, which leads to the extravasation of protein-rich fluid from the perivascular space.[62] These include accumulation of abdominal ascites fluid, with associated abdominal discomfort, and increases in gastrointestinal symptoms, weight gain, and abdominal girth.[61] More severe cases result in abnormalities in coagulation factors, resulting in thromboses due to hemoconcentration.[61,64,65,66,67] Other toxic effects include liver and renal dysfunction,[68] and respiratory distress due to increase in capillary leakage.[61]

Prevention of the severe symptoms associated with OHSS can be accomplished by several means, including withholding the ovulatory dose of human chorionic gonadotropin (hCG).[61,69] Rescue of overstimulation cycles by decreasing gonadotropin administration,[70] follicle aspiration in IVF, or by converted insemination cycles is possible.[61] In these cases, the symptoms of OHSS can be ameliorated with the conversion to IVF and embryo transfer as an alternative to cancellation, or worse, severe illness.[71,72] Unfortunately, none of these measures can guarantee the prevention of OHSS symptoms, merely the alleviation of the worst of them. The best prevention is careful monitoring of individual patients and manipulation of gonadotropin dosages.

The extremely high levels of circulating E_2 in patients with OHSS are thought to contribute to the pathogenesis of this syndrome. The exact etiology of OHSS is not clear, but one hormone known to play an important part, primarily in the fluid shift associated with this condition, is prostaglandin, since indomethacin can prevent or reduce the severity of this symptom.[60,61] As E_2 has been shown to directly stimulate the production of prostaglandins, it has been postulated that the excessive estrogen produced by the large number of follicles present in OHSS patients exacerbates the fluid-related symptoms.[61] Reducing serum E_2 (ie, follicle aspiration) can greatly aid to reducing the severity of OHSS.

EFFECT OF SUPRAPHYSIOLOGICAL E_2 ON REPRODUCTION: BENEFICIAL OR TOXIC?

Although pregnancy rates have improved with use of ovulation-inducing drugs, the question still remains as to the direct impact of pharmacologically high E_2 on follicular development and oocyte maturation. Studies using immunohistochemical localization techniques demonstrated that relatively few, if any, E_2 receptors were expressed in the cumulus, granulosa, and theca cells of primate ovaries.[73] The authors concluded, therefore, that even though E_2 may directly affect oocyte function, this steroid has relatively little effect on follicle growth in humans. More recent work by Hurst and coworkers,[74] however, refuted this conclusion by demonstrating that not only do E_2 receptors exist on human granulosa cells, but also they are functional (CAT detection assay). Often, disturbances in the "normal" hormonal balance results in suboptimal responses, espe-

cially for reproductive processes. Since the response elements for E_2 exist, it is not unreasonable to assume that inasmuch as a reduction in ovarian E_2 may be detrimental to oocyte function,[7,19] supraphysiologically high E_2 levels may also adversely affect pregnancy outcome due to receptor-mediated detrimental effects on follicle and oocyte maturation and fertilization. Except for OHSS, no strong evidence exists for a true toxic effect of ultrahigh E_2; it still may be necessary to rethink the role of E_2, especially when considering those levels achieved during superovulation in patients being treated for anovulation or prior to IVF.

INFERTILITY DRUGS AND CANCER

The long-term safety of these drugs is still controversial. A link between ovulation-inducing agents and ovarian cancer has been suggested by several case studies reporting the development of tumors following drug therapy.[75,76] Patients with a history of breast, endometrial, and ovarian cancer generally display lower circulating LH, but higher E_2. The authors speculate that this might reflect greater LH binding (and subsequent E_2 production) in ovaries for this high-risk population,[77] and these parameters should be evaluated before ovarian stimulation is begun. In patients with no predisposition to ovarian cancer, however, fertility drugs do not stimulate an increase in select tumor-promoting antigens (ie, carcinoembryonic antigens, SCC and CA-125).[78,79] Although some reports have linked ovulation-inducing agents with a higher incidence of ovarian and breast cancer, generally, this relationship is still unclear, and the actual causality has yet to be proven.

SUMMARY

Ovulation induction and superovulation with fertility drugs results in more than just stimulation of multifollicular ovaries. It becomes apparent that a delicate balance in hormones and growth factors exists, which tolerates finite degrees of manipulation. Perturbations of the system can result in detrimental effects on oocyte maturation, fertilization, embryo development, implantation, and gestation. Diseases resulting directly from ovulation induction, such as OHSS, can lead to severe health complications, in some situations resulting in hospitalization and, in rare situations, even death. There are no absolute criteria for the identification of patients who may be at risk for these complications. Careful consideration must be taken when administering ovulation-inducing agents to maximize fertility while minimizing complications.

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