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SEXUALITY, REPRODUCTION & MENOPAUSE



Easing infertility treatment
during uneasy times:

EXPERT STRATEGIES

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DISCLOSURES

Angeline Beltsos, MD, reports that she has received grant/research support and has served as a consultant and on the speakers bureau of EMD Serono, Ferring Pharmaceuticals, and Merck.

Alice Domar, PhD, reports that she has received grant/research support from Johnson & Johnson and has served on the speakers bureau of Merck.

Marcia Hilse, RNC, MSN, reports that she has served on the speakers bureau of Ferring Pharmaceuticals.

Chris Gooder reports that he has served as a consultant to Ferring Pharmaceuticals.

Jeffrey McKeeby, MD, reports that he has received grant/research support from Ferring Pharmaceuticals and Merck; has served as a consultant to EMD Serono, Ferring Pharmaceuticals, and Merck; and has served on the speakers bureau of Ferring Pharmaceuticals.

Ali Nasser, MD, PhD, reports that he has served on the speakers bureau of Ferring Pharmaceuticals.

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Easing infertility treatment during uneasy times: EXPERT STRATEGIES

Given today's economic upheaval and lingering uncertainties, many people are postponing personal plans. The dream of starting a family should not have to be one of them. Leading practitioners in the field of infertility were asked to participate in a roundtable discussion to share their insights on issues their patients face and on surmounting treatment obstacles. The panelists cover such interrelated topics as identifying and reducing sources of stress, ensuring continuity of care, and creating affordability and cost efficiencies.

Alleviating stress in IVF is more important than once thought

DOMAR: Until a few years ago, patient dropout from treatment was widely attributed to one of two factors: limited finances or physician censoring when a prognosis is poor. A number of studies, however, have shown that physician censoring is relatively uncommon and accounts for only about 13% of dropouts.¹ Even in countries with publicly provided insurance, most patients drop out because of stress. In fact, 50% to 65% of patients stop treatment before they have exhausted insurance coverage, primarily because of stress.¹

In a study we conducted in Massachusetts—where insurance covers women under 40 years of age for 6 IVF cycles—38% of women under 40 receiving IVF treatment did not initiate a third cycle.² Among women aged 40 to 42, 68% did not initiate a third cycle.² The reason given was stress. Stress is also likely the reason some patients never start treatment.

In an IVF cycle, the first 2 weeks are usually manageable. It's the last 2 weeks—the waiting—that causes stress. Jacky Boivin has conducted elegant research in which patients tracked their stress levels daily during an IVF cycle.³ Stress increased following embryo transfer and peaked just before the pregnancy test. The stress experienced during this waiting period overwhelms many patients and they discontinue IVF.

Addressing needs of the whole person. We need to think about the whole patient and not just about the physical aspects of the in vitro fertilization cycle. Many patients don't tell anybody, including their mother, they're undergoing an IVF cycle. Patients may wear a brave face for their physicians and then express dis-

tress or even animosity to their nurse or support staff.

At Boston IVF, we have many components in our program to decrease stress for patients as they undergo IVF. Within a month following their first visit with a physician, all patients receive a letter signed by me in which I explain the very normal connection of stress to the IVF process, and describe the resources we offer to decrease that stress—psychology consultations, acupuncture, nutrition counseling, yoga. We also assign one nurse to a patient throughout her cycle. Patients find this continuity of care reassuring.

After the embryo transfer, each patient receives a worksheet I wrote to help alleviate stress during the waiting phase. It dispels such unfounded fears as the possibility of dislodging an embryo while driving over a pothole, and it gives suggestions on how to handle questions from family and friends. We teach relaxation techniques and have a relaxation CD patients can use during the waiting period.

Identifying those at risk for stopping treatment

DOMAR: I would guess that the patients most at risk of dropping out might be the ones who go straight from work-up to IVF—eg, those with severe male factor infertility or bilateral blocked tubes—who have not experienced either oral or injectable medications. Patients express a fair amount of anxiety about injections. I recently counseled a couple going straight to IVF, and as soon as the wife opened the box of medications and syringes, she decided not to go through with it.

Which patients do you think are emotionally vulnerable and likely to drop out of treatment? And are there steps you have taken to try to protect those patients? Dr. Beltsos?

BELTSOS: Sometimes the most fragile

patients can present as very angry. That's their way of handling stress. With some patients, fragility may be obvious, and with others it may be completely off the radar. A patient may sit in your office exhibiting motivation and commitment to the process, and then walk away from it all or visit a different clinic. We have 2 full-time psychologists to help us with all patients, but particularly with those who are fragile. We also work closely with holistic centers, such as Pulling Down the Moon in the Chicago area.

We try to maintain close contact with couples with in-person visits and phone calls, as well as through e-mail. Electronic communication facilitates dialogue during and outside of business hours. If patients are research-

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ing something on the Internet in the middle of the night, they can send me a question and copy the nurse so that everybody is in the loop.

DOMAR: Although using e-mail for patient communications is controversial, I find it to be a very efficient tool. I don't exchange clinical information, but if someone has a specific question, it's better than playing telephone tag.

MCKEEBY: I don't think we do a very good job at identifying vulnerable patients. Yes, there are patients who lash out in anger or display frustration or sadness. But we also miss emotional fragility. The most important tool for me is the question, "How are you doing?" If you open the door, many patients will accept your invitation to talk and will tell you their

needs. I sometimes focus the question: "How do you feel about having to give yourself an injection?"

We also have resources available for comprehensive mind/body support. We often debate the effects of these treatments on pregnancy rates, and there are no clear data on the matter. But patients who receive acupuncture invariably tell me it's the best hour they've spent that week. Reducing stress is what it's all about. We also provide emotional support through social work or psychological consultations. It's important, though, to recommend these latter resources delicately. Many women already feel inadequate in needing help to become pregnant, and we don't want them inferring from our recommendation that they have psychological deficiencies.

NASSERI: Patients who have succeeded in getting pregnant and then experience a pregnancy loss are especially fragile when they return for another IVF cycle. The challenge to them is not just getting pregnant, it's maintaining the pregnancy. Besides notifying the patient's obstetrician, as we do in all cases, we also increase the frequency of contact with the patient even following discharge to her obstetrician to ease the transition period.

DOMAR: Ms. Hilse, from a nurse's perspective, what are some of the support measures that you have in place for patients?

HILSE: Some patients need daily support. Because our practice is so spread out, I may never meet directly with couples so I have had to learn to read a patient's demeanor solely through our phone conversations or e-mails. I think one of the most at-risk groups are patients who avoid sharing what they're going through with their families and employers. With multiple appointments, they may have to be late for work several times and in

today's economy, no one wants to put their job at risk. They may also have to miss family gatherings because of IVF procedures. They simply don't know how to cope with all these things. They don't have a support system as others do. These couples especially depend on their nurses to aid them in defining and strengthening their coping mechanisms.

Innovative ways of reducing patients' cost burden

DOMAR: Another stressful aspect of infertility treatment is its cost, and I'd like to ask Mr. Gooder how he helps patients navigate this issue and the intricacies of insurance coverage.

GOODER: Before patients come to our clinic, they fill out a registration form and receive a phone call from our staff to discuss details of insurance coverage. We review all aspects of the IVF process—consulting, diagnostic testing, specific treatment options—and explain to patients what their insurance will likely cover. When they understand the probable extent of their coverage, we discuss costs.

To help make IVF affordable, we offer a risk-sharing program to couples up to 38 years of age, where they can undergo 3 cycles of IVF for a predetermined cost. They also know that certain aspects of their care will be excluded from that fixed cost—eg, monitoring and medications. We work with ob/gyns in our region, though, to ensure affordable monitoring that is also readily accessible. Insurance companies, too, tend to regard monitoring done by an obstetrician more favorably than monitoring done at a reproductive endocrinology clinic.

Of course, many of our patients do not have insurance coverage either for IVF or for medications or monitoring. Because the least expensive medications for us are Bravelle (uro-

follitropin for injection, purified), Menopur (menotropins for injection, USP), and Endometrin (progesterone) Vaginal Insert, 100 mg, 2 years ago we developed a program with Ferring Pharmaceuticals to make these medications even more affordable for our uninsured patients, who are very appreciative.

In general, costs start to mount by the third cycle, and that can contribute to a patient's decision to drop out. Besides our regular and our fertility-cost-warranty programs, we offer a cost-reduction program where if the first cycle is unsuccessful, we reduce the cost of the second cycle and even the third cycle, if necessary. Our attention to affordability has helped us attract and retain patients, not just from Minnesota but from surrounding states too.

In general, costs start to mount by the third cycle, and that can contribute to a patient's decision to drop out.

DOMAR: Some insurance companies have annual or lifetime caps on infertility coverage. How do you help patients better understand that aspect of infertility insurance coverage?

GOODER: If a cap exists, we ask patients to confirm whether it's a yearly or a lifetime cap, and to learn how much coverage is left. In these cases, coverage is a finite resource, and we try to help patients manage that resource. Although insurance often dictates the use of preferred medications, when given the choice we will usually go with the least expensive medications to stretch a patient's coverage further.

DOMAR: Dr. Nasser, what types of financial programs are you considering in your practice to help attract and

retain patients in these very tough economic times?

NASSERI: The state of New Jersey mandates employers to provide insurance coverage for infertility treatment. Based on our center's experience, the mandate applies to approximately two-thirds of our patients. As many as one-third of our patients do not have coverage for infertility treatment. For these patients, we have discounted packages for all types of treatments: ovulation induction, IVF, donor egg IVF, and frozen embryo transfers. Regardless of the number of visits or the services provided, patients will not be responsible beyond the flat price of the treatment cycle. We are contemplating offering a risk-sharing program that establishes a set fee for a designated number of cycles, and it

would return all or a portion of the fee if pregnancy and delivery is not achieved. We want to be careful, though, that we are not placing excessive financial burden on the better-prognosis patients to subsidize the cost of treatment for the less successful group.

In general, we favor the most affordable gonadotropins and we know which pharmacies provide the best pricing. Patients really appreciate that.

Focusing on simple, patient-friendly treatment protocols

DOMAR: Dr. Beltsos, what else do you as a physician do to support patients throughout their treatment?

BELTSOS: Aside from insurance directives or formulary restrictions, we choose medications according to our treatment protocol, which may vary depending on a patient's medical history. For instance, a protocol for a patient who is a poor responder to gonadotropins may differ from one for a patient with polycystic ovarian syndrome. We also take into account

a patient's experience—what they've used before and what has worked. We often choose medications that can simplify a patient's self-administration. For example, we might start prescribing Bravelle from the start in our OI cycles because we know most of our patients will take Menopur in IVF.⁴ Both products use the same administration technique, a syringe and a device called the Q-Cap,⁵ so patients don't have to worry about learning a second technique such as the pen if they move on to IVF.⁶ It also saves teaching time for nurses.^{6,7} Keeping things simple makes the process more tolerable. It encourages perseverance with repeat cycles. A complicated process is emotionally and financially draining.

MCKEEBY: I agree with Dr. Beltsos, you first must consider a patient's medical history. When you've done that and have an idea of what will provide the best chance of success, consider a patient's personal resource limitations. For some patients, the limitation is financial. For others it may be emotional or physical. The goal is to achieve success with the amount of resources they can muster. Ease of device use is certainly important. The type of injection and the number of injections influence patient acceptability. Particularly with luteal support, choice of medication and its delivery are critical in terms of emotional and physical costs to a patient.

You also have to look at the choice from the nurses' point of view. As you mentioned, Dr. Domar, many practices assign a primary nurse to guide a patient through the process. When you make things easier for the guide, you ease the patient's journey too. And, importantly, if a treatment protocol and injections are easy for the nurse to understand and teach to the patient, you also reduce the number of errors.

DOMAR: Recent research has shown that patients worry a lot about making mistakes.⁸

MCKEEBY: They're extremely worried about it. A certain percentage will call you anytime they think they've made a mistake, even when they haven't. Others are so embarrassed that they don't want you to know. They're afraid you're going to tell them the mistake will negatively affect their outcome. And I don't think they're emotionally ready to hear that.

NASSERI: A typical IVF cycle can require up to 50 injections. As Dr. Beltsos said, when we choose to simplify self-administration and decrease the number of gonadotropin injections for patients, it makes a big difference in how they approach the IVF experience. We are always thinking of ways to reduce the number of injections without compromising treatment outcome.

For example, another means of reducing the number of injections is using vaginally administered progesterone, which works just as effectively as intramuscular formulations.

BELTSOS: Yes, we use vaginal products like Endometrin. Especially with fresh cycles, data suggest that more painful injections do add stress, and the vaginal progesterone product is equally efficacious.^{9,10}

DOMAR: Ms. Hilse, what would you say is your most frequent education challenge when patients are moving from OI to IVF?

HILSE: Our OI cycles usually rely on one type of gonadotropin, but IVF cycles use several different injectable medications and this can be overwhelming for a couple. We try to simplify things at FCI by cutting down on the number of devices a patient has to learn from OI to IVF. For instance, teaching one type of administration for the gonadotropins saves time compared with having to teach multiple techniques.^{6,7} Some patients may be needle phobic, and I might order different medications that allow them to do single injections.

I might do the same for those who do not speak English well and have difficulty understanding the different available administration devices.

It's also important to assure patients that we will provide detailed guidance throughout their cycle. I encourage husbands and wives alike to send e-mails. They often apologize for calling or e-mailing questions and I assure them that's what I'm there for. They need to understand that we expect them to ask questions if things are unclear; that preventing mistakes is easier than correcting them. We make it clear that our role is to guide them through their treatment cycle with as little stress as possible.

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Please see Important Safety Information on page 6.

Indications and Important Safety Information for BRAVELLE® (urofollitropin for injection, purified), MENOPUR® (menotropins for injection), and ENDOMETRIN® (progesterone) Vaginal Insert 100 mg

MENOPUR® (menotropins for injection), administered subcutaneously is indicated for the development of multiple follicles and pregnancy in the ovulatory patients participating in an Assisted Reproductive Technology (ART) program.

BRAVELLE® (urofollitropin for injection, purified) administered SC or IM in conjunction with hCG, is indicated for ovulation induction in patients who have previously received pituitary suppression. BRAVELLE administered SC in conjunction with hCG is indicated for multiple follicular development (controlled ovarian stimulation) during ART cycles in patients who have previously received pituitary suppression.

ENDOMETRIN® (progesterone) Vaginal Insert is indicated to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART treatment program for infertile women.

Important Safety Information

MENOPUR and BRAVELLE are contraindicated in women who have: a high FSH level indicating primary ovarian failure, uncontrolled thyroid and adrenal dysfunction, an organic intracranial lesion such as a pituitary tumor, sex hormone dependent tumors of the reproductive tract and accessory organs, abnormal uterine bleeding of undetermined origin, ovarian cysts or enlargement not due to polycystic ovary syndrome. BRAVELLE is contraindicated in women who have the presence of any cause of infertility other than anovulation. MENOPUR is contraindicated in women who have prior hypersensitivity to menotropins or MENOPUR. BRAVELLE is contraindicated in women with a prior hypersensitivity to urofollitropins, purified. MENOPUR and BRAVELLE are not indicated in women who are pregnant. BRAVELLE may cause fetal harm when administered to a pregnant woman.

ENDOMETRIN should not be used in individuals with any of the following conditions: previous allergic reactions to progesterone or any of the ingredients of ENDOMETRIN, known missed abortion or ectopic pregnancy, liver disease, known or suspected breast cancer, active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.

MENOPUR and BRAVELLE should only be used by physicians who are

thoroughly familiar with infertility problems. MENOPUR and BRAVELLE are potent gonadotropic substances capable of causing Ovarian Hyperstimulation Syndrome (OHSS) (overall IVF incidence of 3.8% for MENOPUR, 6.0% for BRAVELLE), with or without pulmonary or vascular complications, in women undergoing therapy for infertility. Serious pulmonary conditions and thromboembolic events have been reported with MENOPUR and BRAVELLE.

The physician should be alert to earliest signs of myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis. ENDOMETRIN should be discontinued if any of these are suspected.

Patients with a history of depression need to be closely observed when receiving treatment with ENDOMETRIN. Consider discontinuation if symptoms worsen.

ENDOMETRIN should not be recommended for use with other vaginal products (such as antifungal products) as this may alter progesterone release and absorption from the vaginal insert.

Multiple pregnancies have occurred following treatment with MENOPUR and BRAVELLE.

The most common adverse reactions ($\geq 10\%$) reported in IVF clinical trials (N=499) of MENOPUR were headache, abdominal pain, and nausea.

The most common adverse reactions ($\geq 10\%$) reported in an IVF clinical trial and donor IVF study (N=150) of BRAVELLE SC were abdominal cramps and headache.

The most common adverse reactions (greater than 5%) reported in patients receiving ENDOMETRIN were post-oocyte retrieval pain, abdominal pain, nausea, and ovarian hyperstimulation syndrome.

Please see Brief Summaries of Prescribing Information on adjacent pages.

FOR SUBCUTANEOUS AND INTRAMUSCULAR INJECTION

For full prescribing information, see package insert. A brief summary follows.

INDICATIONS AND USAGE: Ovulation Induction: Bravelle[®], administered SC or IM in conjunction with hCG, is indicated for ovulation induction in patients who have previously received pituitary suppression.

Multifollicular Development During ART: Bravelle[®], administered SC in conjunction with hCG, is indicated for multiple follicular development (controlled ovarian stimulation) during ART cycles in patients who have previously received pituitary suppression.

Selection of Patients: 1) Before treatment with Bravelle[®] is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. Except for those patients enrolled in an *in vitro* fertilization program, this should include a hysterosalpingography (to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum (or urine) progesterone, urinary pregnanediol and endometrial biopsy. Patients with tubal pathology should receive Bravelle[®] only if enrolled in an *in vitro* fertilization program. 2) Primary ovarian failure should be excluded by the determination of gonadotropin levels. 3) Careful examination should be made to rule out the presence of an early pregnancy. 4) Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for diagnosis before starting Bravelle[®] therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities. 5) Evaluation of the husband's fertility potential should be included in the workup.

CONTRAINDICATIONS: Bravelle[®] is contraindicated in women who have: 1) A high FSH level indicating primary ovarian failure. 2) Uncontrolled thyroid and adrenal dysfunction. 3) An organic intracranial lesion such as pituitary tumor. 4) The presence of any cause of infertility other than anovulation. 5) Abnormal bleeding of undetermined origin. 6) Ovarian cysts or enlargement not due to polycystic ovary syndrome. 7) Prior hypersensitivity to urofollitropins, purified. 8) Bravelle[®] is contraindicated in women who are pregnant and may cause fetal harm when administered to a pregnant woman. There are limited human data on the effects of Bravelle[®] when administered during pregnancy.

WARNINGS: Bravelle[®] is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) with or without pulmonary or vascular complications in women. Bravelle[®] therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of appropriate monitoring facilities (see **PRECAUTIONS-Laboratory Tests** section). Bravelle[®] should be used with a great deal of care.

Overstimulation of the Ovary During Bravelle[®] Therapy: Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 20% of those treated with follitropin and hCG, and generally regresses without treatment within two or three weeks. In order to minimize the hazard associated with the occasional abnormal ovarian enlargement, which may occur with FSH-hCG therapy, the lowest dose consistent with expectation of good results should be used. Careful monitoring of ovarian response can further minimize the risk of overstimulation. If the ovaries are abnormally enlarged on the last day of Bravelle[®] therapy, hCG should not be administered in the course of therapy; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome.

OHSS: OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see **Pulmonary and Vascular Complications** below). Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the Ovarian Hyperstimulation Syndrome (OHSS).

In a clinical study of ovulation induction, 6 of 72 (8.33%) Bravelle[®]-treated women developed OHSS and two were classified as severe. In a clinical study for multiple follicular development during IVF, 3 of 60 Bravelle[®]-treated women developed OHSS and 1 was classified as severe. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about 7 to 10 days after treatment. Usually, in cases where OHSS may be developing prior to hCG administration (see **PRECAUTIONS-Laboratory Tests**), the hCG should be withheld. If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized. A physician experienced in the management of the syndrome, or who is experienced in the management of fluid and electrolyte imbalances, should be consulted.

Pulmonary and Vascular Complications: Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported following FSH therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple Pregnancies: Multiple pregnancies have occurred following treatment with Bravelle[®] SC and IM. Pregnancy outcomes in a controlled study of 72 patients undergoing ovulation induction with Bravelle[®] were as follows: **Total continuing pregnancies** in patients in the 2 study groups—Bravelle[®] SC (N=9) and Bravelle[®] IM (N=7), respectively—were as follows (patients, or patients/percent, where applicable): Singletons: 3/33.3; 5/71.4; Total number with multiple pregnancies: 6/66.7; 2/28.6; Twins: 4; 0; Triplets: 2; 0; Quadruplets: 0; 1; Quintuplets: 0; 0; Sextuplets: 0; 0; 1.

Pregnancy outcomes in a controlled study of 60 patients undergoing treatment with Bravelle[®] SC in IVF were as follows: Total number of continuing pregnancies (N=23) were as follows (patients, or patients/percent, where applicable): Singletons: 15/65.2; Total number of multiple pregnancies: 8/34.8; Twins: 5; Triplets: 3.

The patient and her partner should be advised of the potential risk of multiple births before starting treatment.

Hypersensitivity/Anaphylactic Reactions: Hypersensitivity/anaphylactic reactions associated with follitropins for injection, purified administration have been reported in some patients. These reactions presented as generalized urticaria, facial edema, angioneurotic edema, and/or dyspnea suggestive of laryngeal edema. The relationship of these symptoms to uncharacterized urinary proteins is uncertain.

PRECAUTIONS: General: Careful attention should be given to the diagnosis of infertility in the selection of candidates for Bravelle[®] therapy (see **INDICATIONS AND USAGE- Selection of Patients** section).

Information for Patients: Prior to therapy with Bravelle[®], patients should be informed of the duration of treatment and the monitoring of their condition that will be required. Possible adverse reactions (see **ADVERSE REACTIONS** section) and the risk of multiple births should also be discussed.

Laboratory Tests: The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestations. The clinical confirmation of ovulation is determined by: a) A rise in basal body temperature; b) Increase in serum progesterone; and c) Menstruation following the shift in basal body temperature. When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following: a) Fluid in the cul-de-sac; b) Ovarian stigmata; and c) Collapsed follicle. Because of the subjectivity of the various tests for the determination of follicular maturation and ovulation, it cannot be overemphasized that the physician should choose tests with which he/she is thoroughly familiar.

Carcinogenesis and Mutagenesis: Long-term toxicity studies in animals and *in vitro* mutagenicity tests have not been performed to evaluate the carcinogenic potential of urofollitropin for injection, purified.

Pregnancy: Pregnancy Category X: See **CONTRAINDICATIONS** section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from Bravelle[®], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients: Safety and effectiveness in pediatric patients have not been established.

Geriatric Patients: Safety and effectiveness in geriatric patients have not been established.

ADVERSE REACTIONS: The safety of Bravelle[®] was examined in four clinical studies that enrolled a total of 222 patients receiving Bravelle[®], including 72 for ovulation induction and 150 for IVF. All adverse events (without regard to causality assessment) occurring $\geq 2\%$ incidence in the clinical study patients receiving Bravelle[®] are listed as follows:

FPI FSH 99-03 Study for Ovulation Induction: All patients with adverse events $\geq 2\%$ for Bravelle[®] SC (N=35) and Bravelle[®] IM (N=37), respectively, were as follows (patients/percent): **Genitourinary/Reproductive:** OHSS: 4/11.4; 2/5.4; Vaginal hemorrhage: 3/8.6; 0/0.0; Ovarian disorder (pain, cyst): 1/2.9; 3/8.1; Urinary tract infection: 0/0.0; 1/2.7; Cervix disorder: 1/2.9; 0/0.0; **Gastrointestinal:** Nausea: 2/5.7; 0/0.0; Enlarged abdomen: 1/2.9; 1/2.7; Abdominal pain: 1/2.9; 2/5.4; Vomiting: 0/0.0; 1/2.7; Constipation: 0/0.0; 1/2.7; Diarrhea: 0/0.0; 0/0.0; **Metabolic/Nutritional:** Dehydration: 0/0.0; 1/2.7; Weight gain: 1/2.9; 0/0.0; **Skin/Appendages:** Acne: 1/2.9; 0/0.0; Exfoliative dermatitis: 0/0.0; 1/2.7; **Other Body Systems:** Headache: 4/11.4; 3/8.1; Pain: 2/5.7; 0/0.0; Neck pain: 0/0.0; 1/2.7; Respiratory disorder: 2/5.7; 0/0.0; Hot flashes: 2/5.7; 0/0.0; Fever: 0/0.0; 1/2.7; Hypertension: 0/0.0; 1/2.7; Emotional lability: 0/0.0; 1/2.7; Depression: 0/0.0; 1/2.7; Accidental injury: 0/0.0; 1/2.7.

Integrated IVF Safety Profile (FPI FSH 99-04, FPI FSH 99-05 and FPI FSH 2001-01 Studies for IVF): All patients with adverse events $\geq 2\%$ for Bravelle[®] SC (N=150) were as follows (patients/percent): **Genitourinary/Reproductive:** Vaginal hemorrhage: 7/4.7; Post retrieval pain: 12/8.0; Pelvic pain/cramps: 10/6.7; OHSS: 9/6.0; Uterine spasms: 4/2.7; Vaginal spotting: 4/2.7; Urinary tract infection: 5/3.3; Ovarian disorder: 3/2.0; Breast tenderness: 3/2.0; Vaginal discharge: 4/2.7; Infection fungal: 3/2.0; **Gastrointestinal:** Abdominal cramps: 21/14.0; Nausea: 13/8.7; Abdominal pain: 7/4.7; Abdominal fullness/enlargement: 10/6.7; Constipation: 3/2.0; **Other Body Systems:** Headache: 19/12.7; Pain: 8/5.3; Rash: 4/2.7; Respiratory disorder: 6/4.0; Sinusitis: 3/2.0; Injection site reaction: 6/4.0; Hot flash: 6/4.0; Emotional lability: 3/2.0.

The following medical events have been reported subsequent to pregnancies resulting from gonadotropin therapy in published clinical studies: 1) Spontaneous abortion. 2) Ectopic pregnancy. 3) Premature labor. 4) Postpartum fever. 5) Congenital abnormalities. The following adverse reactions have been previously reported during urofollitropin for injection, purified therapy: 1) Pulmonary and vascular complications (see **WARNINGS** section). 2) Adnexal torsion (as a complication of ovarian enlargement). 3) Mild to moderate ovarian enlargement. 4) Hemoperitoneum. 5) There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

DRUG ABUSE AND DEPENDENCE: There have been no reports of abuse or dependence with follitropins.

OVERDOSAGE: Aside from possible ovarian hyperstimulation (see **WARNINGS**) and multiple gestations (see **WARNINGS**), little is known concerning the consequences of acute overdosage with Bravelle[®].

HOW SUPPLIED: Bravelle[®] (urofollitropin for injection, purified) is supplied in a sterile, lyophilized, single dose vial containing 82.5 IU of FSH, to deliver 75 IU FSH after reconstituting with the diluent. Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP. 75 IU FSH activity, supplied as:

NDC 55566-8505-2: Box of 5 vials + 5 vials diluent

NDC 55566-8505-6: Box of 5 vials + 5 vials diluent + 5 Q-Cap vial adapters

Lyophilized powder may be stored refrigerated or at room temperature (3° to 25°C/37° to 77°F). Protect from light. Use immediately after reconstitution. Discard unused material.

Rx only

Vials of sterile diluent of 0.9% Sodium Chloride Injection, USP, manufactured for Ferring Pharmaceuticals Inc. Q-Cap[™] manufactured by Bioject Medical Technologies Inc. Tualatin, OR 97062

Manufactured for:
FERRING PHARMACEUTICALS INC.
PARSIPPANY, NJ 07054
By: CARDINAL HEALTH
Albuquerque, New Mexico 87107

6048-04

6-D6048FR-04

08/04

Bravelle[®]
(urofollitropin for injection, purified)

Menopur® (menotropins for injection, USP)

FOR SUBCUTANEOUS INJECTION

For full prescribing information, see package insert.

A brief summary follows.

INDICATIONS AND USAGE: MENOPUR® administered subcutaneously is indicated for the development of multiple follicles and pregnancy in the ovulatory patients participating in an ART program.

Selection of Patients: 1) A thorough gynecologic and endocrinologic evaluation, including an assessment of pelvic anatomy, must be performed before treatment with MENOPUR®. Patients with tubal obstruction should receive MENOPUR® only if enrolled in an IVF program. 2) Primary ovarian failure should be excluded by the determination of gonadotropin levels. 3) Careful examination should be made to rule out the presence of an early pregnancy. 4) Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting MENOPUR® therapy. 5) Evaluation of the partner's fertility potential should be included in the workup.

CONTRAINDICATIONS: MENOPUR® is contraindicated in women who have: 1) A high FSH level indicating primary ovarian failure. 2) Uncontrolled thyroid and adrenal dysfunction. 3) An organic intracranial lesion such as a pituitary tumor. 4) Sex hormone dependent tumors of the reproductive tract and accessory organs. 5) Abnormal uterine bleeding of undetermined origin. 6) Ovarian cysts or enlargement not due to polycystic ovary syndrome. 7) Prior hypersensitivity to menotropins or MENOPUR®. 8) MENOPUR® is not indicated in women who are pregnant. There are limited human data on the effects of menotropins when administered during pregnancy.

WARNINGS: MENOPUR® is a drug that should not be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of appropriate monitoring facilities (see **PRECAUTIONS—Laboratory Tests** section).

Overstimulation of the Ovary During MENOPUR® Therapy: Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 5% to 10% of women treated with menotropins and hCG, and generally regresses without treatment within two or three weeks. The lowest dose consistent with expectation of good results and careful monitoring of ovarian response can further minimize the risk of overstimulation. If the ovaries are abnormally enlarged on the last day of MENOPUR® therapy, hCG should not be administered in this course of treatment; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome (OHSS).

OHSS: OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see **Pulmonary and Vascular Complications** section). Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the OHSS.

In the IVF clinical study, 0399E, OHSS occurred in 7.2% of the 373 MENOPUR®-treated women. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about 7 to 10 days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration (see **PRECAUTIONS—Laboratory Tests** section), the hCG should be withheld. If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized. A physician experienced in the management of the syndrome, or who is experienced in the management of fluid and electrolyte imbalances, should be consulted.

Pulmonary and Vascular Complications: Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from, the OHSS have been reported following menotropins therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple pregnancies: In the clinical trial multiple pregnancy as diagnosed by ultrasound occurred in 35.3% (n=30) of 85 total pregnancies. The patient and her partner should be advised of the potential risk of multiple births before starting treatment.

PRECAUTIONS: General: Careful attention should be given to the diagnosis of infertility in the selection of candidates for MENOPUR® therapy (see **INDICATIONS AND USAGE—Selection of Patients** section).

Information for Patients: Prior to therapy with MENOPUR®, patients should be informed of the duration of treatment and the monitoring of their condition that will be required. Possible adverse reactions (see **ADVERSE REACTIONS** section) and the risk of multiple births should also be discussed.

Laboratory Tests: The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of the OHSS and multiple gestations. The clinical confirmation of ovulation is determined by: a) A rise in basal body temperature; b) Increase in serum progesterone; and c) Menstruation following the shift in basal body temperature. When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following: a) Fluid in the cul-de-sac; b) Ovarian stigmata; and c) Collapsed follicle. Because of the subjectivity of the various tests for the determination of follicular maturation and ovulation, it cannot be overemphasized that the physician should choose tests with which he/she is thoroughly familiar.

Carcinogenesis and Mutagenesis: Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of menotropins.

Pregnancy: Pregnancy Category X: See **CONTRAINDICATIONS** section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if menotropins are administered to a nursing woman.

Pediatric Patients: Safety and effectiveness in pediatric patients have not been established.

Geriatric Patients: Safety and effectiveness in geriatric patients have not been established.

ADVERSE REACTIONS: The safety of MENOPUR® was examined in 3 clinical studies that enrolled a total of 575 patients receiving MENOPUR® in the IVF and OI studies. All adverse events (without regard to causality assessment) occurring at an incidence of ≥2% in women treated with MENOPUR® (adverse events with onset on or after GnRH administration, costart classification) are listed as follows:

IVF (includes IM and SC subjects from protocols MFK/IVF0399E and MENOPUR® 2000-02): Patients (n=499) with adverse events ≥2% were as follows (patients/percent): **Body as a whole:** Abdomen enlarged: 12/2.4; Abdominal cramps: 30/6.0; Abdominal fullness: 16/3.2; Abdominal pain: 88/17.6; Back pain: 16/3.2; Elevated estradiol: 12/2.4; Flu syndrome: 13/2.6; Flushing: 12/2.4; Headache: 170/34.1; Injection site pain: 27/5.4; Injection site reaction: 48/9.6; Malaise: 14/2.8; Pain: 16/3.2; Cardiovascular: Migraine: 12/2.4; Digestive: Constipation: 8/1.6; Diarrhea: 14/2.8; Nausea: 60/12.0; Vomiting: 21/4.2; Nervous: Dizziness: 13/2.6; Respiratory: Cough increased: 8/1.6; Respiratory disorder: 29/5.8; Urogenital: Breast tenderness: 9/1.8; Hot flash: 3/0.6; Menstrual disorder: 16/3.2; OHSS: 19/3.8; Pelvic cramps: 0/0.0; Pelvic discomfort: 2/0.4; Post retrieval pain: 32/6.4; Uterine spasm: 8/1.6.

OI (includes IM and SC subjects from protocol MENOPUR® 2000-01): Patients (n=76) with adverse events ≥2% were as follows (patients/percent): **Body as a whole:** Abdomen enlarged: 0/0.0; Abdominal cramps: 5/6.6; Abdominal fullness: 7/9.2; Abdominal pain: 7/9.2; Back pain: 0/0.0; Elevated estradiol: 0/0.0; Flu syndrome: 1/1.3; Flushing: 0/0.0; Headache: 12/15.8; Injection site pain: 0/0.0; Injection site reaction: 9/11.8; Malaise: 2/2.6; Pain: 2/2.6; Cardiovascular: Migraine: 0/0.0; Digestive: Constipation: 0/0.0; Diarrhea: 2/2.6; Nausea: 6/7.9; Vomiting: 2/2.6; Nervous: Dizziness: 0/0.0; Respiratory: Cough increased: 2/2.6; Respiratory disorder: 3/3.9; Urogenital: Breast tenderness: 2/2.6; Hot flash: 2/2.6; Menstrual disorder: 0/0.0; OHSS: 10/13.2; Pelvic cramps: 3/3.9; Pelvic discomfort: 2/2.6; Post retrieval pain: 0/0.0; Uterine spasm: 3/3.9.

DRUG ABUSE AND DEPENDENCE: There have been no reports of abuse or dependence with menotropins.

OVERDOSAGE: Aside from possible ovarian hyperstimulation (see **WARNINGS** section), little is known concerning the consequences of acute overdosage with MENOPUR®.

HOW SUPPLIED: MENOPUR® (menotropins for injection, USP) is supplied in sterile vials as a lyophilized, white to off-white powder or pellet. Each vial of MENOPUR® is accompanied by a vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

75 IU FSH and 75 IU of LH activity, supplied as:

NDC 55566-7501-1—Box of 5 vials + 5 vials diluent

NDC 55566-7501-2—Box of 5 vials + 5 vials diluent + 5 Q•CAP® vial adapters

STORAGE: Lyophilized powder may be stored refrigerated or at room temperature (3° to 25°C/37° to 77°F). Protect from light. Use immediately after reconstitution. Discard unused material.

Rx only

Vials of sterile diluent of 0.9% Sodium Chloride Injection, USP, manufactured for Ferring Pharmaceuticals Inc.

Manufactured for:
FERRING PHARMACEUTICALS INC.
PARSIPPANY, NJ 07054

By: CARDINAL HEALTH
Albuquerque, New Mexico 87107

6092-02

6-D6092FR-02

APRIL 2010

BRV-04125

FERRING
PHARMACEUTICALS

Endometrin[®]

(progesterone) Vaginal Insert 100mg

Important: For vaginal use only

For full Prescribing Information, see package insert.
A brief summary follows.

INDICATIONS AND USAGE:

Endometrin is indicated to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

CONTRAINDICATIONS:

Endometrin should not be used in individuals with any of the following conditions:

- Previous allergic reactions to progesterone or any of the ingredients of Endometrin
- Known missed abortion or ectopic pregnancy
- Liver disease
- Known or suspected breast cancer
- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events

WARNINGS:

Cardiovascular or Cerebrovascular Disorders

The physician should be alert to earliest signs of myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis. Endometrin should be discontinued if any of these are suspected.

Depression

Patients with a history of depression need to be closely observed. Consider discontinuation if symptoms worsen.

Use of Other Vaginal Products

Endometrin not recommended for use with other vaginal products (such as antifungal products) as this may alter progesterone release and absorption from the vaginal insert.

PRECAUTIONS:

Pregnancy: Endometrin has been used to support embryo implantation and maintain clinical pregnancy in one clinical study. The livebirth outcomes of these pregnancies were as follows:

Among the 404 subjects treated with Endometrin twice daily, 143 subjects had livebirths consisting of 85 singletons, 56 twins, and 2 triplets. In this treatment group, 13 subjects had a spontaneous abortion, 1 subject had an ectopic pregnancy, and 7 subjects reported fetal birth defects (3.4% based on 203 livebirths).

Among the 404 subjects treated with Endometrin three times daily, 155 subjects had livebirths consisting of 91 singletons, 60 twins, and 4 triplets. In this treatment group, 22 subjects had a spontaneous abortion, 4 subjects had an ectopic pregnancy, and 7 subjects reported fetal birth defects (3.1% based on 223 livebirths).

Birth defects reported in the Endometrin twice daily group included: one fetus with a cleft palate and intrauterine growth retardation, one fetus with spina bifida, three fetuses with congenital heart defects, one fetus with an umbilical hernia, and one fetus with an intestinal anomaly.

Birth defects reported in the Endometrin three times daily group included: one fetus with an esophageal fistula, one fetus with hypospadias and an underdeveloped right ear, one fetus with Down's and an atrial septal defect, one fetus with congenital heart anomalies, one fetus with DiGeorge's syndrome, one fetus with a hand deformity, and one fetus with cleft palate.

Nursing Mothers: Detectable amounts of progesterone have been identified in the milk of nursing mothers. The effect of this on the nursing infant has not been determined.

Pediatric Use: This drug is not intended for pediatric use and no clinical data have been collected in children.

Geriatric Use: No clinical data have been collected in patients over age 65.

ADVERSE REACTIONS:

Clinical Studies Experience

The safety data reflect exposure to Endometrin in 808 infertile women (74.9% White, 10.3% Hispanic, 5.4% Black, 5.0% Asian, and 4.6% Other) in a single Assisted Reproductive Technology 10 week clinical study conducted in the U.S. Endometrin was studied at doses of 100 mg twice daily and 100 mg three times daily. The adverse reactions that occurred at a rate greater than or equal to 2% in either Endometrin group are listed as follows:

Endometrin, 100 mg two times daily (N=404)

Gastrointestinal Disorders: Abdominal pain 50 (12%), Nausea 32 (8%), Abdominal distension 18 (4%), Constipation 9 (2%), Vomiting 13 (3%). **General Disorders and Administration Site Reactions:** Fatigue 7 (2%). **Infections and Infestations:** Urinary tract infection 9 (2%). **Injury, Poisoning and Procedural Complications:** Post-oocyte retrieval pain 115 (28%). **Nervous System Disorders:** Headache 15 (4%). **Reproductive System and Breast Disorders:** Ovarian hyperstimulation syndrome 30 (7%), Uterine spasm 15 (4%), Vaginal bleeding 13 (3%).

Endometrin, 100 mg three times daily (N=404)

Gastrointestinal Disorders: Abdominal pain 50 (12%), Nausea 29 (7%), Abdominal distension 17 (4%), Constipation 14 (3%), Vomiting 9 (2%). **General Disorders and Administration Site Reactions:** Fatigue 12 (3%). **Infections and Infestations:** Urinary tract infection 4 (1%). **Injury, Poisoning and Procedural Complications:** Post-oocyte retrieval pain 102 (25%). **Nervous System Disorders:** Headache 13 (3%). **Reproductive System and Breast Disorders:** Ovarian hyperstimulation syndrome 27 (7%), Uterine spasm 11 (3%), Vaginal bleeding 13 (3%).

Expected Adverse Reaction Profile Seen with Progesterone

Endometrin is also expected to have adverse reactions similar to other drugs containing progesterone that may include breast tenderness, bloating, mood swings, irritability, and drowsiness.

OVERDOSAGE: Treatment of overdosage consists of discontinuation of Endometrin together with institution of appropriate symptomatic and supportive care.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Nonclinical toxicity studies to determine the potential of Endometrin to cause carcinogenicity or mutagenicity have not been performed. The effect of Endometrin on fertility has not been evaluated in animals.

HOW SUPPLIED/STORAGE AND HANDLING: Each Endometrin Vaginal Insert is a white to off-white oblong-shaped insert debossed with "FPI" on one side and "100" on the other side. Each Endometrin[®] (progesterone) Vaginal Insert, 100 mg, is packed individually in a sealed foil pouch. These pouches are available in cartons packed:

21 vaginal inserts with 21 disposable vaginal applicators (NDC 55566-6500-3)
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Rx only

Manufactured by:
Pharmaceuticals International Inc., Hunt Valley, MD 21031

Manufactured for:
Ferring Pharmaceuticals Inc., Parsippany, NJ 07054
6323-01

For more information, go to www.endometrin.com.