



FOR WOMEN WHO HAVE PCOS

In laparoscopic ovarian drilling, an insulated needle unipolar electrode is inserted in the ovary perpendicular to the surface to create 6 to 12 evenly spaced punctures using 40 watts of coagulating current for 2 seconds at each point. The mechanism of action is unclear, but it is thought that the destruction of androgen-producing stroma is responsible for the reduction in testosterone level, increase in follicle-stimulating hormone (FSH), and return to FSH cyclicity in 80% of cases.



FERTILITY

Two experts discuss the detrimental reproductive effects of obesity; the challenge of preventing ovarian hyperstimulation; and why 4 million or so “outcomes” validate Prof. Robert Edwards’s Nobel Prize in Physiology or Medicine



» G. David Adamson, MD

Dr. Adamson is Director of Fertility Physicians of Northern California in Palo Alto and San Jose; Adjunct Clinical Professor at Stanford University School of Medicine; Associate Clinical Professor at the University of California, San Francisco, School of Medicine; and Past President of the American Society for Reproductive Medicine.



» Mary E. Abusief, MD

Dr. Abusief is a Board-Certified Specialist in Reproductive Endocrinology and Infertility at Fertility Physicians of Northern California in Palo Alto and San Jose, Calif.

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Impaired fertility is no small problem. According to the Centers for Disease Control and Prevention (CDC), it affects 7.3 million women 15 to 44 years old in the United States alone, or approximately 10% of the female population of reproductive age.¹

Not long ago, there was little to be done about the problem. Today, however, we have many tools and tactics at our disposal, and another CDC statistic demonstrates their efficacy: Fewer than one third of women who have received medical intervention for impaired fertility in the past year continue to experience the problem.¹

In this article, we highlight three recent developments in fertility:

- We know more about the effects of obesity on fecundity, and more about how to increase the likelihood of pregnancy and live birth in obese women
- The development of in vitro fertilization (IVF) more than 30 years ago represents a significant achievement and vast benefit to mankind, noted the Nobel Committee in awarding the 2010 prize for Physiology or Medicine to Robert Edwards, PhD
- Ovarian hyperstimulation syndrome after controlled ovarian stimulation cannot be avoided completely—but its likelihood can be reduced significantly through careful assessment of the patient and a cautious approach to ovarian stimulation.

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Hear Dr. Adamson describe strategies to avert ovarian hyperstimulation, at obgmanagement.com

Be mindful of the effects of obesity on a woman’s reproductive function

Obese patients are almost three times as likely as women of normal weight to be infertile. Polycystic ovarian syndrome (PCOS) is generally unmasked or exacerbated, or both, by obesity, and the hyperandrogenicity associated with PCOS can cause

ovulatory dysfunction. The hypothalamic-pituitary-ovarian (HPO) axis is also affected by overweight and obesity, resulting in oligo-ovulation in 30% to 47% of women.² Some studies suggest that fecundity may be reduced in ovulatory obese women as well



as those with ovulatory dysfunction.² Most obese women are *not* infertile, however.

Once pregnancy is achieved, the risk of miscarriage is elevated in obese women (odds ratio [OR] ~1.67), and the live birth rate is lower (OR ~0.75), compared with women of normal weight.²⁻⁴ Obese women also have an elevated risk of miscarriage after egg donation (OR ~1.52) and ovulation induction (OR ~5.11). There is no evidence that the rate of miscarriage is increased after IVF, compared with other treatments.

The diagnosis of infertility is difficult in obese patients because the pelvic examination is less informative, although ultrasonography (US) is usually helpful.⁵ In addition, obesity can blur the distinction between PCOS and HPO axis-related oligo-ovulation. Laparoscopy and other diagnostic interventions are performed less frequently in obese women, and complications of diagnostic laparoscopy are higher in this population.³

Take the initiative in recommending weight loss

As health-care providers, we need to be more proactive in recommending lifestyle changes for obese women so that they lose weight before pregnancy. Women who have infertility are usually very motivated to conceive; as a result, they may also be motivated to lose weight. Caloric restriction, increased physical activity, behavioral modification, and professional expertise are all essential for successful weight loss.² Even a reduction as small as 5% to 10% of body weight can have clinical benefit.^{2,4,5}

Metformin is an additional option. When combined with a low-calorie diet, metformin may lead to weight loss, restore ovulation, and improve fecundity in women who have PCOS.²

Bariatric surgery is now commonly reserved for women whose body weight is 45 kg or more above normal. Bariatric surgery can improve the altered hormone profile, including elevated thyroid-stimulating hormone (TSH), of obese women. It also appears to improve fecundity and reduce

pregnancy-associated complications. However, it is not always successful and can have complications of its own.

What can you offer to obese patients who experience infertility?

- **Clomiphene citrate** is the most commonly used ovarian-stimulation agent for oligo-ovulation that arises from PCOS or HPO-axis disruption; it is most effective in patients of normal weight.^{4,6} The protocols associated with clomiphene administration in obese patients are similar to those for women of normal weight; so are results, although the pregnancy rate is not as high in obese women.
- **Gonadotropins** are effective ovarian-stimulation drugs that are used in hypothalamic hypogonadal patients as well as after failed treatment with clomiphene citrate. Gonadotropins can be effective even in very obese patients; the dosage increases with body mass index (BMI).^{4,6}
- **Metformin** reduces insulin resistance in women who have PCOS. By itself, metformin is ineffective at inducing ovulation and has not proved to increase the pregnancy rate when it is added to clomiphene.⁵ Nevertheless, it is commonly given at a daily dosage of 1,000 to 2,000 mg to women who have hyperinsulinemia, and it may reduce the miscarriage rate in women who have PCOS.
- Other medications that have been used to enhance ovulation in obese women include **dexamethasone** to reduce elevated androgen levels, **bromocriptine** for elevated prolactin levels, and **thyroid hormone** for hypothyroidism.
- Among obese women who have oligo-ovulation, **ovarian drilling** (FIGURE, page 36) is generally reserved for patients who have not responded to clomiphene or gonadotropins. This procedure has proved to be as effective as clomiphene administration, with the advantage that it does not increase the risk of multiple gestation and leads to longstanding

FAST TRACK

Even a reduction as small as 5% to 10% of body weight can improve fertility



improvement in one third of patients.⁵ Ovarian drilling is a modification of ovarian wedge resection for women who have PCOS. The mechanism of action is not clear, but it is thought that destruction of androgen-producing stroma causes an immediate reduction in testosterone, an increase in follicle-stimulating hormone (FSH), and a return to FSH cyclicity in 80% of cases. These effects can persist for several years, and a pregnancy rate of approximately 60% can be attained in less than 6 months. Clomiphene-resistant women may be more responsive to the drug after ovarian drilling, and the risk of ovarian hyperstimulation appears to be reduced. Ovarian drilling is less effective in obese women than in women of normal weight. Complications include adhesions around the ovary and reduced

ovarian reserve.

- **Assisted reproductive technology (ART)** is sometimes used in this population, but it is less likely to lead to pregnancy and live birth, for unknown reasons.^{2,3} We inform obese women that a BMI below 30 is desirable before ART.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Overall, the management of infertility in obese women is extremely challenging because of its multiple causes—many of which are still not well understood. However, the profound implications of obesity for all aspects of reproduction make it imperative that we pay more attention to identification and treatment of obesity in the infertile population.

IVF is cited by Nobel Committee for its “benefit to mankind”

On December 10, 2010, Robert Edwards, PhD, was awarded the Nobel Prize in

Physiology or Medicine for his innovative and pioneering work to create IVF. In presenting the award, the Committee noted that Professor Edwards’ work “represents a monumental medical advance that can truly be said to confer the greatest benefit to mankind.”

Professor Edwards is the embryologist who performed the basic science and laboratory work, along with Dr. Patrick Steptoe, who provided clinical care, which led to the birth of the world’s first IVF baby, Louise Brown, on July 25, 1978. Since then, IVF has become the most successful treatment for infertility and is available in more than 100 countries. The delivery rate for each single IVF attempt is about 25% globally; it more than doubles in selected patients who have a good prognosis. In some countries, almost 5% of all births arise from IVF; in the United States, that figure is about 1%. The International Committee Monitoring ART (ICMART) estimates that more than



Prof. Robert Edwards (left) holds the infant Louise Brown

PHOTO: GETTY IMAGES

4 million babies have been born from IVF around the world.

Early road was rocky

Despite the broad and significant success of IVF, Professor Edwards struggled for years against scientific and social opposition. His research was opposed by some on ethical and religious grounds, and the United Kingdom refused to fund some of his early work. The initial lack of support for IVF has transformed into acceptance as infertility has been recognized as a disease by many governments and the World Health Organization (WHO). In addition, the Centers for Disease Control and Prevention (CDC) has recognized infertility as a public health issue.

Nevertheless, most insurers still provide inadequate IVF coverage because of misperceptions about infertility and lack of recognition that it is a disease that globally affects 9% of all women of reproductive age, with male-partner sperm problems contributing to the problem in about 50% of cases.

IVF technologies achieve many goals

Over the past 32 years, IVF has revolutionized reproductive medicine and the treatment of infertility and brought an entirely new science to human reproduction.

Specific IVF technologies that have changed the face of medicine include:

- **intracytoplasmic sperm injection** (ICSI) to treat male factor infertility
- **cryopreservation or vitrification of sperm, eggs, and embryos** to allow optimal results from IVF and to help cancer patients have babies after treatment
- **preimplantation genetic diagnosis** (PGD) to prevent major genetic diseases. (For more on PGD, see the January 2009 “Update on Prenatal Counseling” in our archive at www.obgmanagement.com.)

Much scientific research is now directed toward assessing the quality of embryos so that the live birth rate can be increased at the same time that multiple births are reduced. Advances in PGD and stem cell research show great promise for the future of human reproduction and the management of diseases of all organ systems.

WHAT THIS TRIBUTE MEANS FOR PRACTICE

The Nobel Committee’s recognition of Professor Robert Edwards’s extraordinary and visionary accomplishments marks the highest global acknowledgement of the efficacy, safety, and applicability of IVF, as well as its great promise for the future. All physicians should be aware of how this powerful technology can be used in caring for their patients.



More than 4 million babies have been born globally as a result of IVF

Ovarian hyperstimulation can be tempered through strategic management

Controlled ovarian stimulation is pharmacotherapy of the ovaries to produce more than one oocyte in non-ART cycles or to produce multiple oocytes for retrieval at follicular aspiration.⁷ Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, and potentially serious, complication of

controlled ovarian stimulation. With vigilant management, however, its risks and sequelae can be reduced.

Best approach: Prevent OHSS

To reduce a woman’s risk of OHSS, identify



Proposed clinical grading system for OHSS

Criteria	How would OHSS be graded?		
	Mild	Moderate	Severe
Objective findings			
Fluid in pouch of Douglas	✓	✓	✓
Fluid around uterus (major pelvis)		✓	✓
Fluid around intestinal loops			✓
Hematocrit >45%		✓*	✓
White blood cells >15,000/mm ³		±*	✓
Low urine output <600 mL/24 h		±*	✓
Creatinine >1.5 mg/dL		±*	±
Elevated transaminases		±*	±
Clotting disorder			± [†]
Pleural effusion			± [†]
Subjective findings			
Abdominal distention	✓	✓	✓
Pelvic discomfort	✓	✓	✓
Breathing disorder	±**	±**	✓
Acute pain	±**	±**	±**
Nausea and vomiting	±	±	±
Ovarian enlargement	✓	✓	✓
Pregnancy occurrence	±	±	✓

Note: ± indicates that the finding may or may not be present.

* If two of these are present, consider hospitalization

† If present, consider intensive care

** If present, consider hospitalization

SOURCE: Humaidan P, et al.⁹

FAST TRACK

Women who have PCOS have an elevated risk of ovarian hyperstimulation syndrome

her risk factors and employ the appropriate prevention strategies. The list of potential risk factors includes:

- age <33 years
- PCOS or its features
- high antral follicle count
- history of OHSS
- high basal anti-müllerian hormone level
- robust response to ovarian stimulation (≥18 follicles or estrogen level of 5,000 ng/dL, or both).

Once that patient’s risk is established, steps can be taken to judiciously manage her cycle and reduce the likelihood that she will develop OHSS.

Prevention strategies include:

- lowering the dosage of gonadotropin (consider a gonadotropin-releasing hormone [GnRH] antagonist protocol)
- coasting cycles until the estradiol level

plateaus or decreases (reduce the dosage of human chorionic gonadotropin [hCG], use a GnRH agonist trigger for

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The most highly effective strategies for reducing OHSS include use of a GnRH antagonist protocol and use of a GnRH agonist as a trigger. Other prevention strategies, such as metformin administration and cryopreservation of embryos, can further reduce the risk of severe OHSS. Although absolute prevention is impossible, surveillance for risk factors and careful clinical management by all physicians, including, when appropriate, referral to specialists, can reduce the incidence and severity of this dangerous complication.

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In the event of a sexually transmitted disease during Mirena use: Should the patient's relationship cease to be mutually monogamous, or should her partner become HIV positive, or acquire a sexually transmitted disease, she should be instructed to report this change to her clinician immediately. The use of a barrier method as a partial protection against acquiring sexually transmitted diseases should be strongly recommended. Removal of Mirena should be considered.

Mirena should be removed for the following medical reasons:

- New onset menorrhagia and/or metrorrhagia producing anemia
- Sexually transmitted disease
- Pelvic infection; endometritis
- Symptomatic genital actinomycosis
- Intractable pelvic pain
- Severe dyspareunia
- Pregnancy
- Endometrial or cervical malignancy
- Uterine or cervical perforation.

Removal of the system should also be considered if any of the following conditions arise for the first time:

- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
 - Exceptionally severe headache
 - Jaundice
 - Marked increase of blood pressure
 - Severe arterial disease such as stroke or myocardial infarction.
- Removal may be associated with some pain and/or bleeding or neurovascular episodes.

5.14 Glucose Tolerance

Levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Mirena.

6 ADVERSE REACTIONS

The following most serious adverse reactions associated with the use of Mirena are discussed in greater detail in the *Warnings and Precautions* section (5):

- Ectopic Pregnancy [see *Warnings and Precautions* (5.1)]
- Intrauterine Pregnancy [see *Warnings and Precautions* (5.2)]
- Group A streptococcal sepsis (GAS) [see *Warnings and Precautions* (5.3)]
- Pelvic Inflammatory Disease [see *Warnings and Precautions* (5.4)]
- Embedment [see *Warnings and Precautions* (5.6)]
- Perforation [see *Warnings and Precautions* (5.7)]
- Breast Cancer [see *Warnings and Precautions* (5.10)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data provided reflect the experience with the use of Mirena in the adequate and well-controlled studies for contraception (n=2,339) and heavy menstrual bleeding (n=80). For the contraception indication, Mirena was compared to a copper IUD (n=1,855), to another formulation of levonorgestrel intrauterine system (n=390) and to a combined oral contraceptive (n=94) in women 18 to 35 years old. The data cover more than 92,000 woman-months of exposure. For the treatment of heavy menstrual bleeding indication (n=80), the subjects included women aged 26 to 50 with confirmed heavy bleeding and exposed for a median of 183 treatment days of Mirena (range 7 to 295 days). The frequencies of reported adverse drug reactions represent crude incidences.

The adverse reactions seen across the 2 indications overlapped, and are reported using the frequencies from the contraception studies.

The most common adverse reactions (≥5% users) are uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal/pelvic pain (12.8%), ovarian cysts (12%), headache/migraine (7.7%), acne (7.2%), depressed/altered mood (6.4%), menorrhagia (6.3%), breast tenderness/pain (4.9%), vaginal discharge (4.9%) and IUD expulsion (4.9%).

Other relevant adverse reactions occurring in <5% of subjects include nausea, nervousness, vulvovaginitis, dysmenorrhea, back pain, weight increase, decreased libido, cervicitis/Papanicolaou smear normal/class II, hypertension, dyspareunia, anemia, alopecia, skin disorders including eczema, pruritus, rash and urticaria, abdominal distention, hirsutism and edema.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Mirena: device breakage and angioedema. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Manufactured for:
Bayer HealthCare
Pharmaceuticals
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Manufactured in Finland

Bayer HealthCare Pharmaceuticals Mirena Hotline - 1-866-647-3646
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antagonist cycles, and avoid using hCG for luteal support)

- using an insulin-sensitizing agent such as metformin
- cryopreserving embryos for transfer at a later date (consider in vitro maturation instead of standard IVF [experimental]).⁸

OHSS has usually been classified according to the signs and symptoms present.⁹ However, Humaidan and colleagues recently presented a **new classification system for OHSS** that is also based on objective vaginal US and laboratory parameters, as well as volume of fluid shifts (**TABLE**, page 42).⁸

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DID YOU KNOW?

The International Committee Monitoring ART estimates that more than 4 million babies have been born from IVF around the world.

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