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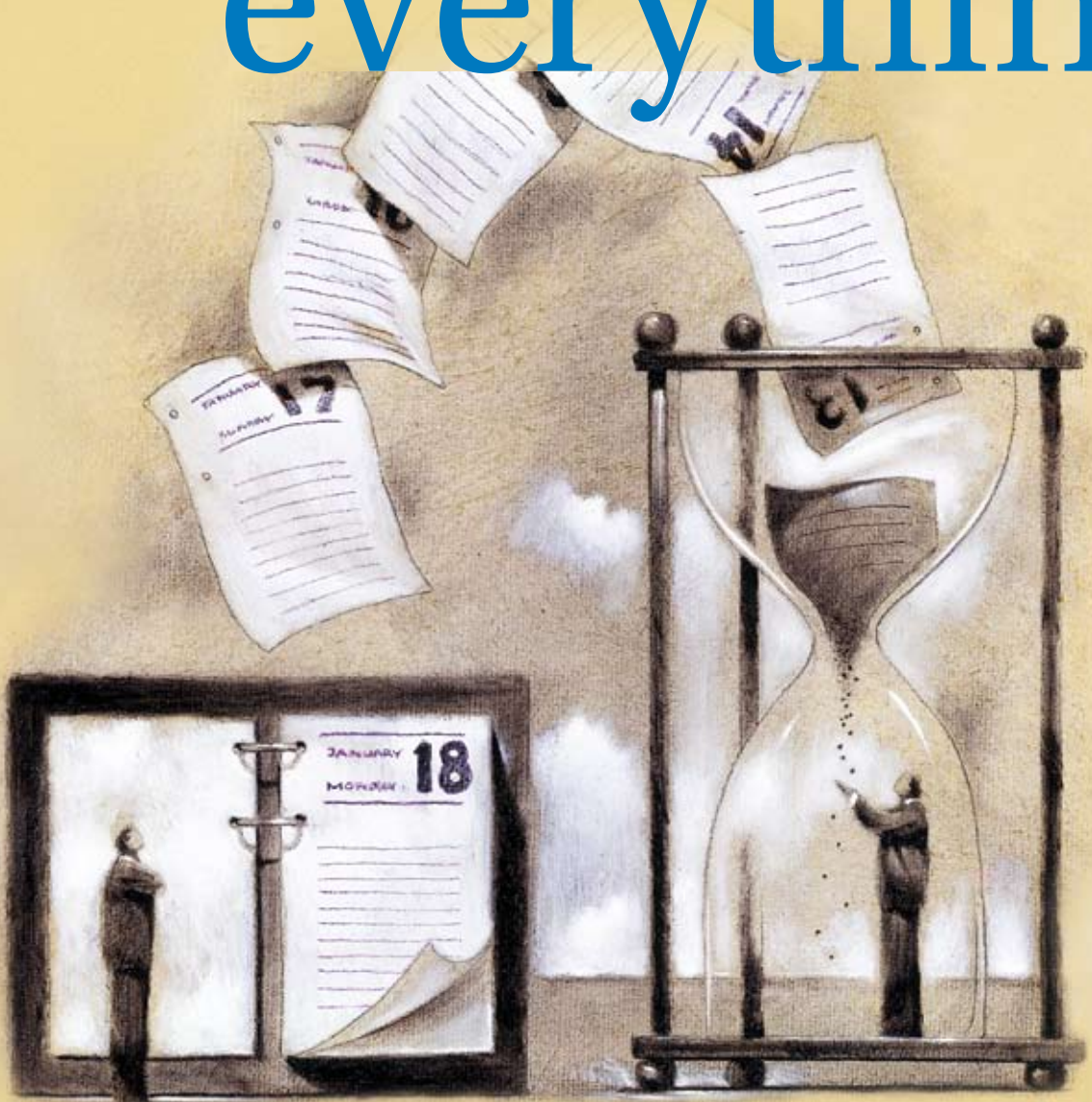
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SEXUALITY, REPRODUCTION & MENOPAUSE

COLLABORATIVE INFERTILITY CARE

Role of ObGyns and reproductive endocrinologists

TIMING is  
everything



# Timing is everything

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## DISCLOSURES

**DR CARSON** reports serving on the medical advisory boards of Columbia Laboratories, Watson Pharmaceuticals, Ferring Pharmaceuticals, EMD Serono, Inc., and Organon, a division of Schering-Plough. She served on the speakers bureau for Ther-Rx Corporation.

**DR KOWALCZYK** reports serving on the speakers bureaus of Ortho Pharmaceuticals and Ferring Pharmaceuticals.

**DR MCGOVERN** reports receiving current grant/research support from Ferring Pharmaceuticals and prior grant/research support from EMD/Serono.

**DR SCHRIOCK** reports serving on the speakers bureaus of EMD/Serono and Organon, a division of Schering-Plough.

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## A roundtable discussion on the collaborative role of ObGyns and reproductive endocrinologists

**A**ccurate identification of infertility and timely referral for specialty care optimizes a patient's chances of becoming pregnant; conversely, unhelpful advice and prolonged trials of unsuccessful treatment can lead to frustration and disappointment all around.

Partnerships between generalist obstetrician-gynecologists (ObGyns) and reproductive endocrinologists (REs) are common in the care of many patients who are seeking to become pregnant. Four reproductive endocrinologists describe their most—and least—successful collaborative efforts with ObGyns and share their thoughts on the optimal timing of referral for infertility treatment and hand-back to the ObGyn.

### Timing the referral

**DR CARSON:** I would like to begin by discussing the situation we hope to avoid: Patients who arrive at the RE's office after trying for years to become pregnant and frustrated that they may have missed an opportunity to get treatment earlier.

**DR KOWALCZYK:** I recently saw a 38-year-old patient who had been trying to conceive for 3 years. She first saw her ObGyn at age 35, who told her to relax and keep trying. A year later, she consulted her preacher, who suggested that she also pray. When she finally came to me for evaluation, her follicle-stimulating hormone (FSH) level was 22 IU/L, and her husband had azoospermia.

Patients like this are often frustrated and regret the years that they lost before being treated. When I counsel such patients, I try to be optimistic. I focus on where we are now and on moving forward, and point out all the options that are still available to them. This patient was able to choose from using a donor egg or embryo, or adoption. I also explained that the situation would not necessarily have been different 3 years ago.

**DR MCGOVERN:** Interestingly, I have rarely seen a patient who was unhappy to be referred for consultation with an RE, even in the most obvious case of premature referral. One woman who came to me had only been trying for 3 months and had nothing wrong. She appreciated our discussion about the normal physiology of reproduction and the menstrual cycle, and the reassurance that "everything seems to be fine."

## Age, medical conditions

**DR CARSON:** How does a patient's age affect the way that you evaluate her?

**DR KOWALCZYK:** For women younger than 35 years, the definition of infertility is a year of trying to become pregnant without success. For women older than 35 years, it is 6 months of trying; for women older than 40 years, it is yesterday. The parameters for evaluation should be performed according to the patient's age category.

With younger patients, it is particularly important to assess for medical causes of infertility. For a 21-year-old who was cycling regularly and had been trying for only a few months, I would explain how to monitor ovulation and outline a plan for further evaluation if she did not become pregnant within a target period of time. If she had irregular periods or a medical history which suggested a cause of infertility, such as Chlamydia, or if there were something in her partner's history, I would evaluate her sooner.

**DR CARSON:** Menstrual cycle irregularities and pelvic pain may indicate the presence of an underlying condition, such as polycystic ovary syndrome (PCOS) or endometriosis. How do you work with generalist ObGyns to treat patients who have medical conditions that cause infertility?

**DR SCHRIOCK:** Treatment of endometriosis is a good example of teamwork with the ObGyn. Our practice primarily treats endometriosis with in vitro fertilization (IVF). When patients need surgical treatment of endometriosis for pain relief or removal of an endometrioma that makes pregnancy risky, their ObGyn usually performs the surgery.

Interestingly, endometriosis advances a woman's ovarian age.<sup>1-4</sup> I would approach treatment of a 33-year-old with an endometrioma as I would treatment of an infertile 35-year-old, particularly if she has had surgery to treat endometriosis or has menstrual cycles that are shorter than 26 days. I encourage such patients to try IVF sooner.

**TABLE**

### Screening test results in potential polycystic ovary syndrome subjects (n=1313)

Criteria for exclusion	Abnormal test/ total subjects tested	Prevalence (%)
Normal serum androgen level	249/1280	19.5
Oligospermia	95/881	10.1
Bilateral tubal blockage	35/839	4.2
Currently pregnant	20/968	2.0
Diabetes	14/902	1.5
Congenital adrenal hyperplasia	10/937	1.1
Hyperprolactinemia	10/993	1.0
Liver disease	8/822	0.9
Uncontrolled thyroid disease	9/985	0.9
Premature menopause	5/985	0.5
Androgen-secreting tumors	1/1038	0.1
Cushing's syndrome	1/1032	0.1

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**DR MCGOVERN:** There is good evidence that patients with menstrual cycles longer than 35 days are anovulatory.<sup>5</sup> It is very reasonable to evaluate such patients to determine the cause of the irregularity and treat them, regardless of age or how long they have been trying, because they are unlikely to conceive if they are not ovulating.

After diagnosis of PCOS, couples often believe that ovulation disturbance is their only problem. When screening participants for the Pregnancy in PCOS trial, more than 10% of the husbands had oligospermia (TABLE).<sup>6</sup> Patients—and clinicians—need to be ready to keep looking beyond the most obvious problem.

## Rescue IVF: Success story

BY ELDON D. SCHRIOCK, MD

A 36-year-old woman with mild oligo-ovulation but an otherwise normal evaluation was treated with gonadotropins by her ObGyn. On day 6, she was hyperstimulated with 9 or 10 follicles that were about to mature.

The ObGyn called our practice and we "fast-tracked" the patient, seeing her the same day using the same protocol as we do for oncology patients. We used an antagonist cycle and were able to perform in vitro fertilization and single embryo transfer, which resulted in a successful pregnancy. Her ObGyn was very happy that she did not have to cancel the cycle and, of course, the patient was pleased with the outcome, so it was a very successful example of a good partnership.

## Basic infertility evaluation

**DR CARSON:** What does your basic infertility evaluation entail for a 30-year-old woman with regular menstrual cycles who has been trying to become pregnant for a year?

**DR KOWALCZYK:** Women younger than 30 may still have decreased ovarian reserve, so I conduct a basic hormonal evaluation: day 3 FSH, thyroid-stimulating hormone (TSH), and prolactin. Laboratory tests and ultrasonic evidence can reveal PCOS in patients without overt symptoms, so if there are subtle issues with ovulation, I add those tests to the workup. I would include a hysterosalpingogram (HSG) to assess uterine cavity defects and tubal patency. In 30% to 40% of cases, male problems contribute to infertility, so a semen analysis should be part of the preliminary evaluation.

**DR MCGOVERN:** We routinely test for estradiol levels and perform an ultrasonic antral follicle count on the same day as our day 3 FSH; patients often come in to test for their day 3 FSH level who are not on day 3 of their cycle. When we do an ultrasound, we realize that they have experienced some bleeding at the time of ovulation and are midcycle. A low antral follicle count also helps to confirm the diagnosis of diminished ovarian reserve.

It is important to note that ovarian reserve screening is done in order to obtain information about the functional age of a woman's ovaries. Functional age is actually more important than chronological age.

**DR SCHRIOCK:** If the estradiol is too high (over 50 pg/mL) or too low (less than 30 pg/mL), it is easy to underestimate the FSH level. In the patient with very short cycles, it is possible that by day 2 or 3 she has already recruited her follicles and her FSH has dropped, so we repeat the test a day earlier in the next cycle.

## When does testing differ?

**DR CARSON:** How would testing differ in a patient who is older than 35 years?

**DR SCHRIOCK:** This patient receives the same tests, but they are done sooner.

**DR KOWALCZYK:** I routinely do a clomiphene citrate challenge test in women older than 35 years to look for any subtle problems with ovarian reserve.

I would also perform this test in a younger patient who has not responded to clomiphene. One of my 26-year-old patients was on clomiphene for 4 months with her ObGyn but did not respond. With the clomiphene citrate challenge test, her day

10 FSH was 15 and her day 3 FSH was 10. The test led her to jump to IVF and not waste time with other treatments.

**DR MCGOVERN:** When the clomiphene citrate challenge test was performed in a mixed-age group of patients with unexplained infertility, young patients had as high a yield as older patients.<sup>7</sup>

We currently use the immunoassay, and that reads about 4 IU/L to 13 IU/L in the normal follicular phase. We consider an FSH level below 10 IU/L to be a good prognosis and 10 IU/L to 15 IU/L to be borderline. At an FSH above 15 IU/L, using a donor egg is the only treatment likely to be successful.

**DR SCHRIOCK:** We consider 8 IU/L or less to be normal and 8 IU/L to 15 IU/L to be borderline. Importantly, these cutoff points do not seem to apply to lesbian patients or single women trying to get pregnant. Surprise pregnancies with a high FSH usually happen in those groups. A heterosexual woman with a partner who has an FSH of 15 is exposed to sperm and might get pregnant before she gets to see me. In contrast, lesbian or single women have fewer eggs that have been exposed to sperm—until they start treatment, of course.

**DR MCGOVERN:** Excellent point. These patients are actually not infertile in the traditional sense that they have had a chance to become pregnant. Almost all data about ovarian reserve and FSH come from studies in infertile women.

**DR SCHRIOCK:** Patients who undergo IVF and embryo biopsy for genetic disease are not infertile in the traditional sense, either, and they seem to follow the same pattern as lesbian and single women.

## Working with women over age 40

**DR CARSON:** How would you approach a 42-year-old woman, with a day 3 FSH of 5 IU/L and an estradiol level of 20 pg/mL, who has been trying to get pregnant for 2 years and is normal on evaluation?

## Pitfalls of empiric therapy: Bilateral tubal blockage

BY PETER G. MCGOVERN, MD

One patient came to my practice after her ObGyn had prescribed 6 months of empiric therapy with clomiphene without an evaluation. When we worked up this patient, the hysterosalpingogram revealed that she had bilateral tubal blockage. She was unhappy to have undergone 6 months of unnecessary and unhelpful therapy.

At a minimum, a trial of empiric clomiphene should be accompanied by some assessment of ovulation and ovarian reserve, a semen analysis, and proof of normal anatomy. However, I generally believe that use of empiric clomiphene is ill-advised, because clomiphene therapy may have more adverse effects in the ovulatory patient on cervical mucus and the endometrium than benefit in terms follicular stimulation.

**DR MCGOVERN:** Age is a factor for this patient, but she has no other definable cause of infertility and normal results on ovarian reserve screening. Unfortunately, our experience is that such patients frequently respond poorly to medication, so I would recommend aggressive therapy for this patient. I would discuss IVF and egg donation and present her with the success rates. If she were interested in less aggressive treatment, I would recommend a clomiphene challenge to uncover any problems with ovarian function that were not detected with the day 3 FSH test.

**DR KOWALCZYK:** I would give her choices of intrauterine insemination with gonadotropin therapy, IVF, or using a donor egg. In my opinion, clomiphene is probably a waste of her time.

**DR SCHRIOCK:** I would repeat the FSH test to be sure that it was not incorrect. I would only encourage her to consider clomiphene if it would help her make a decision about treatment. I would present “what if” scenarios: If you try clomiphene and your FSH is still 5, would you then try gonadotropins? If it is 10, would you decide to try IVF? If it is 20, would you consider a donor egg? Sometimes this helps patients make a decision. If a patient says she wants to do IVF regardless of her FSH, then trying clomiphene would probably be a waste of a cycle.

## Who should do the tests?

**DR CARSON:** Ideally, which tests would a referring physician perform and which do you prefer to do yourself?

**DR KOWALCZYK:** I like to do my own HSGs for several reasons. Patients seem to find HSGs more comfortable when performed by a gynecologist rather than a radiologist. I like to be able to provide patients with immediate feedback about their structural status and when there is something subtle, I prefer to be looking at the x-ray myself. Finally, in my experience, ultrasonographers in a fertility office are more highly attuned to

## If at first you don't succeed... try something completely different

BY CAROLE L. KOWALCZYK, MD

I recently saw a 38-year-old patient who had been trying to conceive for 3 years. She first saw her ObGyn at age 35, who told her to relax and keep trying. A year later, she consulted her preacher, who suggested that she also pray. When she finally came to me for evaluation, her follicle-stimulating hormone (FSH) level was 22 IU/L, and her husband had azoospermia.

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mapping that ovary for antral follicle counts than are ultrasonographers elsewhere.

**DR MCGOVERN:** If a patient has an HSG performed elsewhere, we always ask her to bring a copy of the films or a disk so that we can look at it ourselves.

**DR SCHRIOCK:** I am happy when the ObGyn has already done a semen analysis and evaluated the TSH and prolactin levels. I also like to do my own ultrasound for antral follicle counts and, especially, endometrial assessment; we do that when the patient is preovulatory so that we can do an antral count, dominant follicle assessment, and endometrial assessment with one sonogram.

The ObGyns with whom we partner conduct a normal preconception check-up: They screen for cystic fibrosis, rubella, and varicella; order a complete blood count; assess blood type; conduct any appropriate genetic tests; and remind the patient to take folic acid.

**DR CARSON:** Do you find that patients referred to you have had a lot of unnecessary testing?

**DR SCHRIOCK:** HSGs are sometimes done prematurely, often because insurance carriers require them before a patient can see an RE. In our area, we have been able to negotiate that

requirement away. Some referring physicians require that patients conduct repeated postcoital tests, which can be a waste of time.

**DR MCGOVERN:** In my opinion, the bigger problem is a lack of ordering appropriate tests. I have treated patients who have been trying to get pregnant for 2 to 3 years and then treated with clomiphene for 6 months by their primary ObGyn before they are referred to us. We then determine that the patient was susceptible to rubella or a cystic fibrosis carrier for all of that time. When we explain the issue to the couple, they usually ask us why this wasn't checked earlier. I do not understand why ObGyns frequently do not send a prenatal panel when a couple begins trying to conceive.

## Role of insurance

**DR CARSON:** How do you determine whether to encourage a patient to try a few cycles of gonadotropins and intrauterine insemination (IUI) versus IVF? Does it depend on your FSH, estradiol, and antral follicle count or is it driven by the patient's insurance company?

**DR KOWALCZYK:** At every single consultation, I am asked: What does my insurance cover? What do I have to pay out of pocket? IVF coverage is not man-

dated in Michigan, and people tend to choose what their insurance covers.

Although patients 35 years or older are encouraged to try more aggressive therapies, many decline to use IVF or gonadotropins right away. In that case, I would certainly only continue less successful therapies for 3 months or so.

**DR SCHRIOCK:** We rarely use combined protocols, such as clomiphene and gonadotropins. In a patient with an antral follicle count less than 6, use of a gonadotropin with IUI may improve her chances as much as IVF would. The major problem that IVF cannot fix is an egg problem, so I use those laboratory tests to decide if IVF is really worth the extra cost. Otherwise, we'll do an aggressive gonadotropin cycle and save her money for a possible egg donor cycle.

## Receiving referrals

**DR CARSON:** How do referring ObGyns in your area hear about your practice?

**DR SCHRIOCK:** We frequently hold grand rounds at the hospital. Additionally, we publish a newsletter, *Fertility Flash*, throughout the year. Local ObGyns receive it electronically or in print, and it has become a very popular educational tool because it contains regular updates. ObGyns who call the office are fast-tracked: There is always a physician who can take their call right away.

When educational tools for physicians fail to convey the importance of making that referral, then patient education about the alternatives is necessary. Web pages are helpful, and word-

of-mouth drives much of our traffic.

**DR KOWALCZYK:** I find that ObGyns are increasingly taking the lead in discussing a woman's plans to have children. The topic is becoming less taboo between patients and physicians, and among patients and their peers.

## Hand-back to ObGyns

**DR CARSON:** So many of these referral relationships are important. And having said that, when do you send the patient back to their referring physician?

**DR SCHRIOCK:** We send as many patients as possible back to their referring physicians for surgical procedures and prenatal care. I think that makes ObGyns comfortable about sending the patient to us in the first place.

**DR CARSON:** How have you dealt with ObGyns who just do not want to work with you?

**DR SCHRIOCK:** Some ObGyns may be reluctant to send patients for fertility treatment because they fear having another multiples pregnancy to care for. We perform single embryo transfers in 60% to 70% of the patients in our egg donor program, and we emphasize this when we talk with local ObGyns. It is wonderful when a referring ObGyn prepares a patient by explaining that she might be a good candidate for a single embryo transfer.

**DR KOWALCZYK:** The ObGyns who know the most about fertility evaluation and treatment are the most likely to feel like part of a team and confident in their consultation.

## Conclusion

Infertility is emotionally and financially stressful to patients. Teamwork between ObGyns and REs can maximize the benefits of treatment for a patient through timely referrals and sharing the resources available in each practice. Nearly all fertility clinics have counselors who can help patients manage their stress, and some have specialists to answer insurance questions. ObGyns can initiate infertility evaluation, offer surgical expertise for treatment of conditions such as endometriosis, and provide obstetrical care after successful fertility treatment. Familiarity with local resources, infertility evaluation and treatment practices, and good communication foster the most successful partnerships. ■

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