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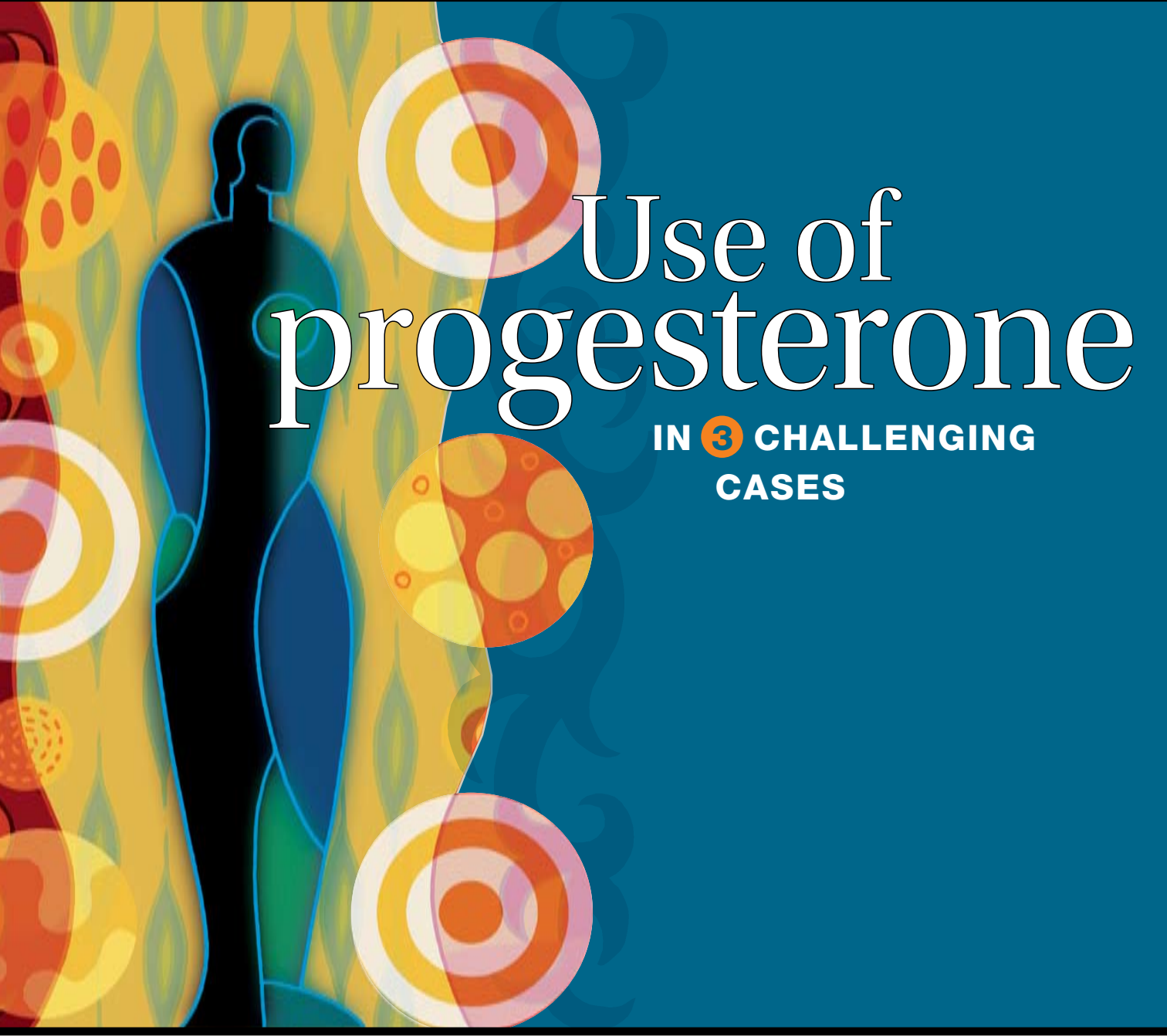
Based on a multidisciplinary panel discussion of case-based practical issues in the use of progesterone therapy, which occurred on June 11, 2008.

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Use of progesterone

IN **3** CHALLENGING
CASES



NPWH
Nurse Practitioners in Women's Health

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education. The American Society for Reproductive Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of health professionals who care for women from adolescence to postmenopause.

EDUCATIONAL OBJECTIVES

At the conclusion of the educational activity, participants should be able to:

- Discuss the potential effects and implications that progestins or progesterone have on the endometrium
- Distinguish differences among synthetic progestins and progesterone, with varying side-effect profiles and methods of administration
- Explain to patients how benefits and risks may affect them individually, based on their unique profile, before drawing conclusions or recommending hormone therapy

ACCREDITATION STATEMENT

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DISCLOSURE

- **Dr Valerie L. Baker** reports that she has received a grant/research support from IBSA.
- **Dr Sandra A. Carson** reports that she has served as a consultant for Watson Labs and Columbia Research Labs and served on the speakers' bureau of Ther-Rx.
- **Dr James H. Liu** reports that he served as a consultant to Barr, Solvay and Novogyne and received a grant/research support from Barr-Duramed, Solvay, and Procter & Gamble.
- **Ms Susan Wysocki** reports that she has served on the advisory boards of Ortho Women's Health, Bayer HealthCare, Digene, Duramed, Lilly, Wyeth, Merck, and Upsher-Smith. She has also served on the speakers' bureau of Bayer HealthCare, Duramed, Organon, Wyeth, and Ther-Rx.

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INTRODUCTION

In this monograph, a multidisciplinary panel discusses case-based practical issues in the use of progesterone therapy, addressing such challenging questions as:

- *When administering progesterone to support early pregnancy during in vitro fertilization, what protocols for initiating and continuing treatment should clinicians follow, in the absence of evidence?*
- *What counsel should clinicians provide when*

confronted with patients who have concerns about hormone therapy and a desire for compounded creams?

- *What are the options clinicians can consider when treating an obese patient with secondary amenorrhea and multiple comorbidities?*

Moderated by Sandra A. Carson, MD, this group of experts reviews pertinent medical studies and offers insight into their own clinical practices.

CASE 1

PROGESTERONE USE IN ASSISTED REPRODUCTIVE TECHNOLOGY

PRESENTED BY VALERIE L. BAKER, MD

Sarah is 39 years old, gravida 0, undergoing in vitro fertilization (IVF) for mild male factor infertility and diminished ovarian reserve. Three gonadotropin cycles with intrauterine insemination have failed. A recent saline infusion sonogram revealed a normal uterine cavity. Sarah has undergone an IVF cycle using a gonadotropin-releasing hormone (GnRH) antagonist, recombinant follicle-stimulating hormone (FSH), urinary human menopausal gonadotropin, and intramuscular progesterone. Unfortunately, no pregnancy occurred in this cycle, despite the transfer of 3 good-quality embryos.

Sarah found the intramuscular (IM) progesterone shots administered by her husband very painful and stressful. She is concerned because her husband will be traveling frequently during their next cycle. However, she is willing to do whatever will give her the best chance of success.

Necessity of progesterone during IVF

DR CARSON: What is the purpose of using progesterone during an IVF cycle?

DR BAKER: Progesterone is required for the success of early pregnancy. If the corpus luteum is removed during the first 5 weeks after conception, the pregnancy will miscarry. By about 9 weeks' gestation, the luteal-placental shift takes place: the trophoblast itself makes sufficient progesterone, and the pregnancy is no longer dependent on the corpus luteum.¹

There are several hypotheses explaining the need

for progesterone administration during an IVF cycle. GnRH agonists and GnRH antagonists are commonly used to prevent ovulation. Either medication may suppress pituitary production of luteinizing hormone (LH), which is required for progesterone production. In addition, during oocyte retrieval, some of the granulosa cells lining the follicles are removed or disrupted, which may be another reason why luteal-phase supplementation is needed in an IVF cycle.

The most recent Cochrane review found higher ongoing pregnancy rates after embryo transfer with progesterone compared with placebo or no treatment,² and it is now routine to recommend luteal-phase support during an IVF cycle. Some clinicians also recommend progesterone supplementation during the natural cycle for women of more advanced age, like Sarah, but there are no solid data to support this practice.

DR CARSON: Should progesterone supplementation differ based on whether a patient has received a GnRH agonist or a GnRH antagonist?

DR BAKER: A GnRH antagonist has a shorter half-life and does not suppress LH for as long a period as a GnRH agonist does, so it had been suggested that there would be no need for luteal-phase supplementation in cycles utilizing a GnRH antagonist. There are fewer studies of antagonist cycles than agonist cycles because these medications have not been used as long. However, compelling data show that pregnancy rates are significantly compromised in GnRH antagonist cycles if the

TABLE 1

Randomized Prospective Studies Comparing P₄ With hCG ± P₄ for Luteal-Phase Supplementation

Trials	Luteal Support	Conclusion
Claman (1992); Golan (1993)	hCG vs IM P ₄	Higher live birth rate with hCG (not significant)
Araujo (1994); Martinez (2000); Ludwig (2001)	hCG vs IM P ₄	No difference in ongoing pregnancy rates
Artini (1995); Martinez (2000); Ludwig (2001)	hCG vs vaginal P ₄	No difference in ongoing pregnancy rates
Buvat (1990)	hCG vs oral P ₄	Higher pregnancy rate with hCG
Fujimoto (2002)	(hCG + IM P ₄) vs IM P ₄	Higher pregnancy rate with the (hCG + IM P ₄) combination
Mochtar (1996); Ludwig (2001)	(hCG + vaginal P ₄) vs vaginal P ₄	No difference in pregnancy rates

hCG, human chorionic gonadotropin; IM, intramuscular; P₄ progesterone. Reprinted with permission from *Fertil Steril*. Vol 89. Hubayter ZR, Muasher SJ. Luteal supplementation in in vitro fertilization: more questions than answers. pp 749-758. © 2008 with permission from Elsevier.

luteal phase is not supported.³ Beckers et al showed that when luteal-phase support was not given in cycles that utilized a GnRH antagonist, there was an overall ongoing pregnancy rate of only 7.5% and poor progesterone production in the later part of the luteal phase.

When human chorionic gonadotropin (hCG) is given to trigger the maturation of the oocytes, some hCG remains in circulation and continues to stimulate the corpus luteal production of progesterone. However, that effect wears off after a few days. If a GnRH antagonist is used without supplementation, these patients will have low progesterone levels as the hCG clears.

Some unresolved issues include whether or not it would be better to supplement with a combination of progesterone and hCG. This combination would theoretically allow better function of the corpus luteum but may be associated with a higher risk of hyperstimulation syndrome. There are other products of the corpus luteum that may be important in early pregnancy. However, there are no good data currently to indicate that luteal phase support with hCG or estradiol improves live birth rate with IVF over progesterone alone (TABLE 1).

DR LIU: Other mechanisms may help explain why using an antagonist would require progesterone support. Studies suggest there are GnRH receptors in the ovary,⁴ so the GnRH analog may have its own effect on the ovary.

Route of administration: Key differences

DR CARSON: Progesterone can be given orally, intramuscularly, or vaginally. What are the differences among the routes of administration?

DR LIU: The metabolism of progesterone differs depending on how it is administered. Oral preparations generally have less biological effect on the endometrium than other forms. Micronization of oral progesterone powder improves its absorption by increasing the surface area of the progesterone molecule to the microvilli in the gastrointestinal tract. However, oral preparations are subject to the first-pass effect through the liver, and their metabolic derivatives do not have the same biological potency for binding to the progesterone receptor.

Intramuscular (IM) progesterone is absorbed directly into the bloodstream and is absorbed by progesterone target tissues before it is metabolized by the liver. IM progesterone clears rapidly; the amounts given are much higher than what the corpus luteum would make daily, which typically peaks around 25 mg/day. We usually give a 50-mg standard dose to IVF patients to provide a safety margin.

Vaginal preparations are absorbed rapidly by the vaginal tissues and lymphatic system and also do not pass through the liver first. Endometrial biopsies show that progesterone content in the endometrium after administration of a vaginal preparation is much higher than levels in the peripheral blood,⁵ suggesting some advantages of nonoral preparations in this situation.¹

DR CARSON: Do these preparations have equal efficacy for pregnancy when given in an IVF cycle?

DR LIU: The IM and vaginal preparations appear to be very similar,² but there is substantial variation among the compounded vaginal preparations used across different studies. There are not as many data on oral preparations, but they do not appear to be as efficacious.

DR BAKER: When a pharmaceutical company is seeking FDA approval of a progesterone preparation, the comparator has to be one that has been approved by the FDA. So far, the only standardized and FDA-approved vaginal preparations are a progesterone gel 8% and a new progesterone vaginal insert 100 mg. These FDA-approved vaginal products are being compared to intramuscular progesterone in studies that are not part of the FDA approval process.

Protocols for starting and stopping progesterone

DR CARSON: When do you start progesterone during an IVF cycle, and how long do you continue?

DR BAKER: The answers to these questions are not completely clear. Many people believe that starting progesterone too early, such as on the day of egg retrieval or earlier, could advance development of the endometrium and make it less receptive by the time the embryo is transferred. Clinicians generally initiate progesterone supplementation after oocyte retrieval but before embryo transfer.

One study found that when progesterone administration was started the day after egg retrieval, IM progesterone was superior to vaginal progesterone in terms of clinical pregnancy rates.⁶ However, the interim report of a follow-up study found no difference between IM and vaginal formulas when IM progesterone was initiated 24 hours after egg retrieval compared with 8% vaginal gel initiated 48 hours after egg retrieval.⁷

A recent, large study evaluating the efficacy and safety of a vaginal insert also started progesterone support the day after egg retrieval,⁸ so I think that is very common timing. When using thrice-daily dosing of vaginal progesterone, some clinicians may not begin until the evening of the day after retrieval (ie, skipping the morning and afternoon doses on that first day), but that is not an evidence-based practice.

CASE 2

USE OF PROGESTERONE IN HORMONE THERAPY

**PRESENTED BY SUSAN WYSOCKI,
RN, WHNP, FAANP**

Jackie is 54 years old and has been taking low-dose combination oral hormone therapy (HT) for 12 months. Prior to using HT, she experienced 13 hot flashes per day, woke up at least 4 times a night with night sweats, and described her symptoms as "making her life miserable." She decided to use HT because she believed that the alternative of

Although the most critical time for progesterone support in an IVF cycle is up to the diagnosis of pregnancy—2 to 3 weeks after oocyte retrieval—clinicians commonly continue supplementation until a gestational age of 8 to 12 weeks. Although there may not be good data supporting this practice, it has evolved because clinicians know that spontaneous miscarriage most commonly occurs in the first trimester. Patients and physicians sometimes associate a miscarriage with discontinuation of progesterone, even if the relationship between the 2 events is not causal.

Safety of progesterone

DR CARSON: Are there risks to the fetus when using progesterone therapy in assisted reproductive technology?

DR LIU: There have been some isolated reports of adverse effects such as hypospadias with exposure to synthetic progestins that are derived from androgens. These include norethindrone and ethisterone, which are used in oral contraceptives. However, the ASRM practice committee found very little evidence supporting a link between natural progesterone products and hypospadias.¹

Case study follow-up

DR BAKER: Although Sarah had had local side effects from the IM progesterone, she chose it over a proposed vaginal preparation for her next cycle, based on her perception of potentially improved efficacy. However, when her husband began traveling for his job, she switched to a vaginal preparation and did achieve a pregnancy. Her physician told her she could safely discontinue progesterone at a gestation age of 8 weeks, but she chose to continue until the end of the first trimester.

This case underscores the fact that much of what we do with progesterone supplementation and assisted reproduction has evolved based on patient preferences and physician concerns, rather than on evidence.

"living with the symptoms wasn't worth it."

For a while, the HT had improved her menopausal symptoms, but recently her hot flashes returned, along with moodiness and irritability. When she tried to discontinue her medications, the hot flashes and night sweats became unbearable and she resumed HT.

Jackie started reading about HT on the Internet and has begun to wonder whether the combination of hormones

she is taking carries more risks than some of the alternatives. A friend told her that compounded hormonal creams have bioidentical hormones that are “like what the body makes” and, therefore, have fewer risks.

From the Internet, Jackie learned that these compounded preparations are adjusted to her hormone levels by salivary testing. She thinks this may be the reason why her symptoms are coming back with her existing HT regimen. When she visits the office, she asks for a test of her hormone levels and a prescription for a compounded product.

Evaluating the claims about compounded preparations

DR CARSON: What are the differences between compounded hormones and those approved by the FDA?

MS WYSOCKI: Compounded hormonal products are not regulated for dosage consistency or purity by the FDA. They do not come with package inserts, warnings, or class labeling, all of which accompany FDA-approved products. The absence of labeling does not mean that the compounds are necessarily safe. In fact, the FDA has recently chastised several compounding pharmacies about deceptive advertising practices.⁹

DR CARSON: What about the use of salivary testing?

MS WYSOCKI: No data support the use of salivary testing to measure the effects of estrogen or progesterone on target tissues anywhere in the body.¹⁰ Even blood tests are not reliable measures of activity at any target tissue. The best bioassay is the patient’s description of her symptoms.

Selecting an HT regimen

DR CARSON: Which route of administration do you prefer for HT?

DR BAKER: I typically recommend a transdermal estradiol patch as a first choice for the delivery of estrogen. There are also a number of preparations, including sprays, lotions, and gels, that have come on the market in recent years as alternative forms of transdermal estrogen administration.

The transdermal route avoids first-pass metabolism in the liver and, therefore, is the most physiologic, which is appealing if our goal is to replace hormones that the ovary would naturally make. Transdermal delivery allows a more consistent level of estradiol in the bloodstream than does oral administration.

Oral estrogen has other potential drawbacks, such as increasing sex hormone-binding globulin, which may affect the bioavailability of testosterone and

estradiol. Oral estrogen can also increase triglyceride levels and may have a slight pro-coagulant effect. Case control studies suggest that transdermal estradiol does not increase risk of venous thromboembolism as much as oral estrogen does,¹¹ although FDA labeling makes no distinction regarding the safety of these preparations.

DR CARSON: What progesterone therapy regimen do you use when a patient still has a uterus?

DR BAKER: I generally favor oral micronized progesterone, 200 mg, for 12 days each cycle, because it has been shown to protect the endometrium and there is not a commercially available transdermal preparation of progesterone.

MS WYSOCKI: It is important to note, also, that compounded progesterone used transdermally has not been shown to have sufficient absorption to provide uterine protection.

Terminology: Bioequivalent, bioidentical

DR CARSON: What is the difference between bioequivalent and bioidentical hormonal compounds?

DR LIU: These terms are often used interchangeably and probably mean different things to different people. Bioidentical means that the structure of the compound is the same as what exists in nature. In that sense, the estradiol in the patch and in some of the transcutaneous preparations are identical.

Bioequivalence refers to a biological effect and means that different compounds have the same ability to target symptoms, such as hot flashes or changes in uterine lining. It is very difficult to say that one preparation is bioequivalent to another, especially if it is given by a different route. What I can say is that, for example, all 0.1-mg estradiol patches are bioequivalent: they deliver the same amount of estrogen into the circulation over the life span of each patch.

Case study follow-up

MS WYSOCKI: Jackie received a 50-mcg estradiol patch and micronized progesterone in the regimen suggested by Dr Baker: 200 mg for 12 days, every 28-day cycle. At her next appointment 3 months later, her hot flashes and night sweats were under control and she was pleased with her regimen.

It is important to note that when Jackie’s low-dose oral HT no longer worked, changing the route of administration alleviated her symptoms; it was not necessary to increase the dose.

CASE 3

MANAGEMENT OF SECONDARY AMENORRHEA

PRESENTED BY JAMES H. LIU, MD

Nicole is 27 years old, gravida 0, with a long history of obesity and great difficulty losing weight. She reports having irregular menstrual cycles ranging from 45 days to 6 months apart. Her last menstrual period was 5 months ago, when she had a heavy menses that lasted 2 weeks. Her body mass index is 42 kg/m², which is considered morbid obesity. Nicole has a large abdominal pannus and normal blood pressure. She has scattered acne lesions on her face and upper back and acanthosis nigricans, a dark pigmentation around the neck and the axilla. Acanthosis nigricans is a biomarker for insulin resistance and high circulating insulin levels.

Nicole's pelvic exam showed a normal vagina and cervix, but it was not possible to palpate her uterus or ovaries because of her abdominal girth. Transvaginal ultrasound found an endometrial thickness of 22 mm. Her ovaries appeared to be multicystic but had normal ovarian volumes. We performed an endometrial biopsy because of concerns about the long duration of unopposed estrogen exposure. The biopsy revealed complex hyperplasia with no atypia.

A lipid profile demonstrated cholesterol 245 mg/dL low-density lipoprotein cholesterol of 180 mg/dL and triglyceride levels of 259 mg/dL. This patient demonstrates many features we see with increasing frequency in reproductive-aged women as we deal with the obesity epidemic.

A complicated diagnosis

DR CARSON: What was your diagnosis, Dr Liu?

DR LIU: Nicole's abdominal obesity, high triglycerides, and evidence of insulin-resistance constituted metabolic syndrome. Although there are many different criteria for this, we used those of the National Cholesterol Education Program (TABLE 2).¹²

DR CARSON: What is her long-term prognosis?

DR LIU: If she is not treated, Nicole would be unable to achieve pregnancy because she does not ovulate and she may have an increased risk of endometrial cancer. Her obesity would eventually cause increasing insulin levels, exhaustion of her pancreatic insulin secretion, and type 2 diabetes. Her obesity might also result in osteoarthritis and difficulty with mobility. Her lipid levels confer increased risk of hypertension and cardiovascular events.

TABLE 2

Components of Metabolic Syndrome Related to Cardiovascular Disease

Abdominal obesity
Atherogenic dyslipidemia
Elevated blood pressure
Insulin resistance ± glucose intolerance
Proinflammatory state
Prothrombotic state

Grundey SM, et al. *Circulation*. 2002;106:3143-3421.

Selecting a treatment strategy: Considerations

DR CARSON: If this patient does not desire pregnancy, what are some treatment options to prevent or treat the endometrial hyperplasia?

DR LIU: Short-term treatment for endometrial hyperplasia involves administration of progesterone or progestins for at least 2 weeks per month for 3 months, with a follow-up endometrial biopsy.

DRBAKER: Nicole also needs protection against endometrial hyperplasia even after this episode is addressed. Oral contraceptives are frequently used for long-term treatment, although there might be concern about the risk of deep vein thrombosis (DVT), particularly in obese or morbidly obese patients and older patients who smoke.

If this patient were not a candidate for oral contraceptives, progesterone or a progestin would typically be administered for approximately 2 weeks each month to prevent recurrence of the hyperplasia. Patients who do not desire a monthly withdrawal bleed can take progesterone every 2 to 3 months.

Patients who are being treated with a progestogen for amenorrhea and hyperplasia may occasionally ovulate. They should be counseled that an alternative form of contraception, such as condoms, are needed to avoid pregnancy.

Dr Liu, would you consider using an intrauterine device (IUD) for this patient?

DR LIU: Certainly, we have individuals using a levonorgestrel-containing IUD. One challenge we have faced

with some of our obese patients is difficultly accessing the cervix for placement.

MS WYSOCKI: Something I've done to improve access to the cervix is to cut off the end of a condom and slip it on to the speculum. When the speculum opens, it pushes the vaginal walls back.

Case study follow-up

DR LIU: Nicole received norethindrone, 5 mg, a strong

progestin, for 2 weeks and had a withdrawal flow for 3 months in a row. Her repeat endometrial biopsy showed a normal endometrium. She still did not ovulate, and since she was not sexually active at that time, she elected to use progesterone, 200 mg, for 14 days every 2 months.

We treated her acne with topical clindamycin gel and she joined our supervised diet and exercise program. She is considering bariatric surgery but must participate in the lifestyle program for at least 6 months in order to qualify.

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RECOMMENDED READING

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