Bruinsma F, Lumley J, Tan J, Quinn M. Precancerous changes in the cervix and risk of subsequent preterm birth. BJOG. 2007;114:70–80.

Q. Does cervical dysplasia raise the risk of preterm birth?

A. Yes—and the risk is elevated whether or not the cervical lesions are treated, although it is higher among treated women. As for the treatments themselves, cone biopsy, loop electrosurgical excision procedure (LEEP), and diathermy were all associated with preterm birth, while laser ablation was not.

EXPERT COMMENTARY

John M. Thorp Jr, MD, Hugh McAllister Distinguished Professor of Obstetrics and Gynecology, and Interim and Deputy Director, Center for Women's Health Research, University of North Carolina School of Medicine, Chapel Hill.

Preterm birth and cervical dysplasia share many risk factors, most of which are the progeny of low socioeconomic status. It is not surprising, therefore, that cervical dysplasia is a risk factor for preterm birth independent of the treatment modality chosen for the precancerous condition. This large cohort study linking outpatient gynecologic records with childbirths from Australia found exactly that. It is the largest study so far to focus on pregnancy outcomes in women following diagnosis and treatment of dysplasia. Frustrating to both the obstetrician and the gynecologist is the fact that smoking is the only readily modifiable risk factor for preterm birth or cervical dysplasia.

Ablative procedures produce better pregnancy outcomes than excision

Beyond epidemiology, this paper bears an important message for clinicians and patients: Procedures that remove portions of the cervix, such as LEEP, diathermy, and cone biopsy, raise the risk of subsequent preterm birth, compared with less destructive ablative procedures such as laser ablation (as reported in the Update on Cervical Disease, by Thomas C. Wright, MD, in the March issue of this journal). This was also demonstrated in a large review of the subject.[1] Therefore, for an optimal obstetrical outcome, ablative procedures are preferable to excisional ones in women who have not yet completed childbearing. Given that success rates are only slightly lower for ablative procedures than for destructive ones, a clinician can recommend ablation without fear of dysplasia progressing to invasive cancer.

Widespread HPV vaccination could help reduce preterm birth rate

This study highlights how a systematic program of human papillomavirus (HPV) vaccination in adolescents (male and female) before their coital debut could reduce the rate of preterm birth by eliminating the need for women to undergo excisional treatment for cervical dysplasia. The possibility for such improvement in birth outcomes should motivate those of us working to prevent preterm birth to advocate for societal investment in this approach. It also might alleviate concerns that HPV vaccination has the potential to disrupt family life by encouraging promiscuity. How can anyone argue against a program that will prevent cancer *and* preterm birth?

Reference

1. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive lesions: a systematic review and meta-analysis of the literature. Lancet. 2006;367:489–498.

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***FAST** TRACK*

Ablative procedures for cervical dysplasia are preferable to excisional ones in women who plan to have more children

Q. Which is best for PCOS-related infertility: clomiphene or metformin?

Legro RS, Barnhart HX, Schlaff WD, et al, for the Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007;356:551–566.

A. Clomiphene is superior to metformin in achieving live births in infertile women with polycystic ovary syndrome (PCOS), but carries a higher risk of multiple gestation.

EXPERT COMMENTARY

John F. Randolph Jr, MD, Professor of Obstetrics and Gynecology, Director of the Division of Reproductive Endocrinology and Infertility, and Director of the Fellowship in Reproductive Endocrinology and Infertility, University of Michigan Health System, Ann Arbor, Mich.

Frontline therapy for ovulation induction in women with PCOS has evolved from clomiphene to metformin, particularly since Palomba and colleagues[1] noted comparable ovulation rates and improved conception rates when metformin was given. This new report by Legro and colleagues from the Cooperative Multicenter Reproductive Medicine Network resoundingly contradicts that more limited report and reasserts the primacy of clomiphene in ovulation induction for PCOS. It is reminiscent of the Women's Health Initiative, in that a well-designed large clinical trial has yielded findings opposite those theorized by investigators.

Legro and colleagues also report a reassuringly low multiple-pregnancy rate in the treatment groups that included clomiphene citrate, and no multiples in the metformin-only group. In addition, they demonstrate a clear, deleterious effect of extreme obesity (body mass index [BMI] greater than 35) on the efficacy of clomiphene and metformin individually and of the 2 agents combined.

Distinctive features of this trial

It is worth noting that the trial by Legro and colleagues contrasts the study by Palomba and associates in 2 critical design characteristics. First, Palomba and associates included only women with a BMI less than 30, whereas Legro and colleagues included a range of body sizes: Only 30% of participants were less than obese and nearly half were massively obese.

Second, the Palomba study was conducted in Italy, presumably in a more homogeneous population than the multiethnic, multicenter trial by Legro and colleagues. However, in the latter trial, even the subgroup analysis for the 179 subjects with a BMI less than 30 demonstrated the same relative proportions of ovulation and conception as the overall trial, albeit with higher rates than in heavier women.

The 2 studies also used slightly different criteria to document ovulation, and the study by Legro and colleagues used the more robust outcome of live birth rate as a primary endpoint—a much more clinically useful measure.

Nonetheless, these differences are insufficient to explain the striking contrast between the data from Legro and colleagues and virtually all of the limited recent work in this area, calling into question the recent move toward metformin as primary frontline therapy. The size, design, and multicenter nature of this trial demand that we consider it the primary source for level I evidence on the subject.

The greater the obesity, the lower the fertility

Perhaps an equally important finding of this study is the diminished response to metformin, clomiphene, or both in women with a BMI of 35 or above. This suggests that aggressive therapy up front may be warranted in these pa-

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Women who have a body mass index of ≥35 have a diminished response to metformin and clomiphene, alone and in combination

tients in addition to a coordinated plan of dietary and exercise therapy.

Bottom line: Use clomiphene first

This study points us back to the long-standing practice of using clomiphene citrate as frontline therapy for ovulation induction in women with PCOS, with the additional caveat that body size is a critical modifier of this therapy. However, the cumulative ovulation rate of about 40% and cumulative conception rate of about 20% in women with a BMI less than 35 taking metformin make that drug a reasonable frontline option for couples very concerned about multiple gestation or significant side effects with clomiphene. ■

Reference

1. Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90:4068–4074.

gravidas who are in no way prepared to handle the responsibilities of pregnancy or parenthood. The psychological stress these women are under should not be underestimated as a possible cause of preterm labor. Many of these women don't even realize how stressful their life is.

We need to educate our young about the responsibility involved in raising a child, and we need to encourage the media and entertainment community to start sending the message that sex is not to be taken lightly but leads to very serious responsibilities.

Jerome A. Klobutcher, MD
Des Plaines, Ill

Dr. Barbieri responds:

Until more data come in, avoid magnesium sulfate

I appreciate the perspectives provided by Dr. Toofanian and Dr. Klobutcher, as well as by Dr. Daniels and colleagues. As experienced clinicians, they all clearly recognize how difficult and frustrating it is to treat the multifactorial causes of prematurity, including the contribution of complex environmental factors such as psychosocial stress in the mother.

I agree with Dr. Toofanian that multimodal treatment of preterm labor might delay birth, but that great care must be taken to avoid adverse effects, such as maternal pulmonary edema.

Dr. Daniels and associates are correct that we need additional studies comparing magnesium sulfate to a placebo for the treatment of preterm labor. Until additional data indicate the effectiveness of magnesium, it is my "subjective" opinion that patients in preterm labor are best served by treatment with nifedipine, a β-agonist, or indomethacin. A continuing concern is that magnesium sulfate treatment of preterm labor, especially at dosages greater than 2 g/h, may be associated with adverse newborn outcomes. ■