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OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

# Why Are Cesarean Delivery Rates Higher With IVF Pregnancies?

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**Dr. Rebar reports no financial relationships relevant to this field of study.**

SYNOPSIS: The major factors leading to increased odds of cesarean delivery in all infertile women, but particularly in those who conceive following in vitro fertilization, are advanced maternal age and previous uterine surgery.

SOURCE: Stern JE, et al. Factors associated with increased odds of cesarean delivery in ART pregnancies. *Fertil Steril* 2018;110:429-436.

To determine why the incidence of cesarean deliveries is greater in women with pregnancies resulting from in vitro fertilization (IVF) than in fertile pregnant women, Stern et al retrospectively compared singleton deliveries from primiparous women in Massachusetts between 2004 and 2010. To acquire the data, the investigators linked the Massachusetts vital and hospital records to the Society for Assisted Reproductive Technology (SART) Clinic Outcome Reporting System. During the years studied, there were six to eight clinics performing IVF in Massachusetts, and all reported their outcome data to SART. Of the 173,130 deliveries in Massachusetts, 5,768 followed IVF, 2,657 occurred in infertile women who did not undergo IVF, and 164,705 occurred in fertile pregnancies. Of the deliveries, 117,743 were vaginal and 55,387 were by cesarean delivery. The rates of cesarean delivery were 45.7%, 43.3%, and 31.1% in the IVF-treated women, infertile women not undergoing IVF, and fertile women, respectively. The women undergoing IVF were older, more often white and non-Hispanic, and more apt to have private insurance, prior uterine surgery, gestational diabetes, hypertension during the pregnancy, bleeding, and placental abnormalities than fertile women. The same was true for the infertile women who did not undergo IVF. The unadjusted odds ratios (ORs) compared with fertile women were 1.84 (95% confidence interval [CI], 1.75-1.94) for IVF-treated and 1.68 (95% CI, 1.55-1.81) for infertile women who did not undergo IVF. After adjustment for demographics, underlying medical factors, previous uterine surgery, and placental and delivery complications, the adjusted odds ratios (aORs) compared with fertile women were

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1.27 (95% CI, 1.19-1.36) for IVF-treated and 1.15 (95% CI, 1.04-1.27) for infertile women not undergoing IVF. The strongest confounders for odds of cesarean delivery were age and previous uterine surgery.

## ■ COMMENTARY

It is clear that the odds of cesarean delivery is higher among infertile women and those undergoing IVF.[1-3] It also is known that infertile women and especially those undergoing IVF have an increased risk of both maternal and fetal morbidity.[3,4] This study adds to our understanding of why.

Not surprisingly, infertile women who conceive either with or without IVF are older. Consequently, they are much more apt to have chronic disorders such as diabetes, hypertension, and obesity. Moreover, they are more apt to have undergone abdominal or uterine surgery, especially myomectomy, conization, operative hysteroscopy, and endometriosis. It is not surprising that the strongest confounders in this study predisposing to cesarean delivery were age and previous uterine surgery. The increased odds for cesarean delivery also probably are the result of infertile women asking for elective cesarean delivery.[5] Some women choose this route of delivery despite being advised that cesarean delivery is associated with increased maternal morbidity[5,6] and possible negative effects on the infant.[7] It may well be that women with pregnancies resulting from IVF and their physicians elect cesarean delivery because of the much greater investment of time and money in achieving pregnancy. It may be that physicians feel more comfortable ensuring an optimal outcome by recommending elective cesarean delivery or elect to proceed with cesarean delivery at the first hint of any problem during labor. It also is known that advanced maternal age is associated with increased stillbirths and is a risk factor for cesarean delivery.[6] In any case, it is certainly true from this study that the rates of cesarean delivery were higher among infertile women.

It is also interesting to note that cesarean delivery rates were significantly higher in all infertile women, regardless of whether they underwent IVF to achieve pregnancy. In fact, although cesarean deliveries were significantly more frequent after IVF than in other infertile women, the major increase was observed in infertile women regardless of how they conceived. In retrospect, this too should be obvious if advanced age and prior uterine surgery are the major risk factors in all infertile women. So why did I choose to highlight this particular study? It is simply because all healthcare providers caring for these women should be aware that infertile women are at increased risk during their pregnancies and should be monitored closely. I think that is a lesson well worth remembering. ■

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## ABSTRACT & COMMENTARY

# Childhood Obesity: A Risk Factor for Infertility?

***By Jeffrey T. Jensen, MD, MPH, Editor***

SYNOPSIS: Results from a 25-year prospective study demonstrate a moderate association between childhood obesity before age 12 years and female infertility in adulthood.

SOURCE: He Y, et al. Association of childhood obesity with female infertility in adulthood: A 25-year follow-up study. *Fertil Steril* 2018;110:596-604.

To examine the association between childhood obesity and infertility in adulthood, He et al used a large population-based prospective database from Australia. In 1985, researchers enrolled 8,498 children (4,191 girls) in the Australian Schools Health and Fitness Survey (ASHFS), a nationally representative sample of Australian school children between 7 and 15 years of age. All of these children had physical assessments (body mass index [BMI], waist-to-height ratio). Those 9 to 15 years of age completed questionnaires evaluating lifestyle and cardiovascular risk factors.[1] To better evaluate how health and fitness in childhood affect the development of disease during adulthood, the authors of the Childhood Determinants of Adult Health (CDAH) study took advantage of this large database. From 2002-2004, researchers traced 3,412 female former participants (then 26-36 years of age) from the ASHFS; 2,734 women agreed to participate in the CDAH study and received questionnaires from 2004-2006 (CDAH1) and 2009-2011 (CDAH2). Adult weight and height were measured in clinics during CDAH1, and participants also provided self-reported measurements that allowed investigators to calculate a correction factor. During CDAH2, weight was self-reported only.

A total of 1,754 women provided details on reproductive health questions at least once during CDAH1 or CDAH2. These included detailed questions on female and male infertility. The investigators considered a number of covariate measures, including age at menarche, socioeconomic status, education, smoking, alcohol consumption, and total physical activity as potential confounders. After excluding 210 women missing data on confounders, the final analysis included 1,544 women.

Compared to those with normal childhood weight between the ages of 7 and 11 years, women with childhood obesity were more likely to report infertility (adjusted relative risk [aRR], 2.94; 95% confidence interval [CI], 1.48-5.84), having ever tried to become pregnant without succeeding for > 12 months (aRR 3.89; 95% CI, 1.95-7.77), or having seen a doctor because of trouble becoming pregnant (aRR, 3.65; 95% CI, 1.90-7.02). However, these same associations were not seen among adult women with childhood obesity between the ages of 12 and 15 years. Adult infertility also occurred more commonly among underweight compared to normal-weight girls 7 to 11 years of age. This resulted in a U-shaped association of BMI z scores, with the risk of adult infertility significantly higher among children with z scores > 1.05 or < -0.80. Childhood waist-to-hip ratio at either age grouping also was not associated with infertility.

Based on the results of this prospective study, the authors concluded that among girls, childhood obesity before age 12 years increases the risk of adult infertility.

## ■ COMMENTARY

Although we can't change our patients' childhoods, we might influence the way they raise their own children. We live in a world that seems increasingly scary to parents. Most adults my age remember spending large amounts of time playing outside with a pack of neighborhood kids. We also remember physical education class every day in middle and high school. Although few organized sports existed except Little League, physical activity included walking or riding bikes everywhere you needed to go. Today, most parents discourage kids from walking or biking on roads because of heavy traffic (in part caused by the many parents taking kids to and from activities by car). Our digital world also reduces the incentive to go out and experience the real world. High-calorie beverages and foods contribute to childhood obesity. Since adults make decisions about food purchases, it is not surprising that childhood obesity rates have risen with the adult obesity epidemic. Parents of overweight children tend not to perceive them as overweight, but they are sensitive to concerns about future weight-related health risks.[2]

This study by He et al provides high-quality evidence that early childhood obesity increases the risk of adult infertility. The prospective nature of the study, and adjustment for confounders, allows for the calculation of infertility incidence and relative risks. Unlike so many studies with weak associations (e.g., risk estimates < 2.0), all of the adjusted RRs in this study for obesity in girls younger than 12 years of age hovered around 3.0, indicating a moderate association. Those women who remained consistently obese from 12 years and younger through adulthood had a significantly higher risk of infertility than those who consistently maintained normal body weight. The authors also found that childhood BMI before age 12 years and the risk of adult infertility followed a U-shaped curve, with higher rates of infertility at both extremes. A 2007 study reported a similar U-shaped curve with adolescent BMI and fertility in Finland.[3]

How might early childhood obesity influence adult infertility? Female rats fed an obesogenic diet from weaning developed a reduced number of oocytes and preantral follicles and did not show preovulatory progesterone and luteinizing hormone surges.[4] Studies in humans have shown early-onset obesity associated with early puberty and abnormal maturation of the hypothalamic-pituitary-ovarian axis.[5] These changes may lead to the development of polycystic ovarian syndrome. Once cyclicity begins, the system may be more resilient, as suggested by the lack of association of later onset childhood obesity and infertility in this study.

We live in a society that values diversity and tolerance. This makes us stronger and better. However, this also prevents many of us from commenting on obesity in children out of fear of seeming insensitive. But childhood obesity affects health directly and reduces productivity and longevity. We now have evidence that childhood obesity affects future fertility. Commenting on the health effects of childhood obesity is not insensitive. Your patients' grandchildren may thank you for getting involved. ■

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ABSTRACT & COMMENTARY

# Premature Rupture of Membranes Revisited

***By John C. Hobbins, MD***

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**Dr. Hobbins reports no financial relationships relevant to this field of study.**

SYNOPSIS: An individual participant data meta-analysis from Australia suggests that expectant management of patients with premature rupture of membranes between 34 and 36 weeks, compared with immediate intervention, results in comparable levels of composite neonatal adverse outcomes but in mixed maternal adverse outcomes that balance out in the final analysis.

SOURCE: Quist-Nelson J, et al. Immediate delivery compared with expectant management in late preterm prelabor rupture of membranes: An individual participant data meta-analysis. *Obstet Gynecol* 2018;131:269-279.

Preterm (before 37 weeks) premature (before labor begins) rupture of the membranes (PPROM) occurs in 3% of pregnancies. In these pregnancies, the clinician faces a conundrum regarding whether to move forward with the delivery or to allow further time for in utero maturity. Based on all the information at hand, in the absence of infection, the American College of Obstetricians and Gynecologists (ACOG) recommended in its recent practice bulletin that expectant management be employed when PPROM happens prior to 34 weeks.[1] However, after that time the authors favored delivery. The thrust to deliver mostly has been to avoid neonatal sepsis, but many other potential morbidities fall into play with either option.

Investigators from Australia searched the literature for randomized, controlled trials (RCTs) that would provide individual participant data for meta-analysis. They only included those trials in which individual patient data could be mined from the published papers or obtained directly from the authors.

The primary outcome was a composite of immediate adverse neonatal outcomes, as well as neonatal sepsis, necrotizing enterocolitis, respiratory distress syndrome (RDS), or neonatal death. Secondary outcomes involved individual contributions to the composite. Maternal outcomes included need for cesarean delivery, antepartum hemorrhage, endometritis, and length of hospitalization. All patients in the meta-analysis had vaginal cultures for a variety of agents, including gram-positive beta *Streptococcus* (GBS).

Eight trials were eligible but five did not have individual patient data available, leaving three to yield adequate information on 2,563 patients with PPROM at 34 to 36 weeks. Of these, 1,289 patients were randomized to have immediate delivery and 1,281 had expectant management up until 37 weeks, after which they were delivered. Seventy-six percent of the "immediate" group and 78% of the "expectant" group received antibiotics.

Regarding the primary outcome, there were no significant differences in composite neonatal adverse outcome (9.6% vs. 8.3%; relative risk [RR], 1.20; 95% confidence interval [CI], 0.94-1.55). Also, no differences were noted in overall neonatal sepsis (2.6% vs. 3.5%; RR, 0.74; 95% CI, 0.47-1.15). However, immediate delivery resulted in significantly higher rates of RDS and hyperbilirubinemia. There were no differences in perinatal deaths, but immediate delivery resulted in higher rates of admission to the neonatal intensive care unit (NICU) and longer hospital stays. Mothers having immediate delivery were less likely to have antenatal hemorrhage and chorioamnionitis but had a higher cesarean delivery rate. Interestingly, in those with positive vaginal cultures at randomization, immediate delivery was less likely to be associated with neonatal sepsis (6.5% vs. 23%; RR, 0.35; 95% CI, 0.14-0.86). However, in the 15% and 17% of those who were culture-positive for GBS, there were no significant differences in neonatal sepsis between groups.

## ■ COMMENTARY

Who would have thought that PPROM was so complicated? We still ponder what causes it and wrestle with how to handle it. The obvious answer to the first question is that something weakens the membranes. However, there is no single "something" responsible. Studies certainly have shown that infection with a resulting increase in inflammatory cytokines, such as tumor necrosis factor and interleukins 1 and 6,[2] is involved. Also, elevations of metalloproteinase,[3] an enzyme found in amniotic fluid and fetal blood, imply that the fetus plays at least some role in PPROM. Finally, as far back as 2002, researchers found a failure of normal trophoblastic invasion of the myometrial portion of spiral arteries in the basal plate of placentas in PPROM, like that seen in preeclampsia.[4] This suggests

that a disruption of placentation occurs long before the membranes rupture. So, there is more to the problem than simply mechanically weak membranes.

On to the question of what to do about PPROM when it happens. Earlier studies showed that up until 34 weeks, watchful waiting in PPROM was associated with better outcomes than early intervention. However, between 34 and 36 weeks, opinions vary. The featured meta-analysis found no difference in the authors' primary outcomes, including overall neonatal sepsis, although the outcomes of admissions to the NICU, hyperbilirubinemia, and RDS were seen more commonly with early intervention. In contrast, women in the expectant group had higher rates of chorioamnionitis and antepartum hemorrhage, but had a lower cesarean delivery rate. Overall, the outcome differences between the two methods seem to cancel out each other, resulting in a standoff. This implies that the move to intervene in PPROM between 34 and 36 weeks, as advocated by ACOG, now can be challenged by this meta-analysis, which points toward watchful waiting as a viable option. For brevity, this Alert will not deal with steroids, tocolytics, or antibiotics, but here are some suggestions for management of PPROM:

- If documented rupture of membranes occurs prior to 34 weeks, expectant management seems to be associated with fewer adverse effects, since prematurity trumps the potential for infection.
- In PPROM between 34 and 36 weeks, there appears to be no difference in overall outcomes with either immediate intervention or expectant management, but each case needs to be assessed individually.
- After 36 weeks, the risk of infection from PPROM outweighs any benefit of watchful waiting at that point; if spontaneous labor does not ensue, induction would be warranted.

In some clinical scenarios, it is useful to know the approximate length of time between membrane rupture and when spontaneous labor tends to ensue. In general, the earlier in pregnancy PPROM occurs, the longer the latent period. However, a lesser-known study has shown that if the cervical length, assessed with transvaginal ultrasound, is < 2.0 cm, the average lag time to spontaneous labor is 59 hours, compared with 10 days if the cervical length is > 2.0 cm.[5] ■

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ABSTRACT & COMMENTARY

# Nocturia: Does Salt Intake Play a Role?


***By Chiara Ghetti, MD***

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**Dr. Ghetti reports no financial relationships relevant to this field of study.**



SYNOPSIS: Researchers suggest that excessive salt intake can contribute to urinary frequency and nocturia.


SOURCE: Matsuo T, et al. Daily salt intake is an independent risk factor for pollakiuria and nocturia. *Int J Urol* 2017;24:384-389.

The objective of this study was to identify the relationship between daily salt intake and lower urinary tract symptoms. This was a cross-sectional study of patients with lower urinary tract symptoms admitted to Nagasaki University Hospital in Japan for nonurinary diagnoses. Patients with any condition that affects urinary function were excluded, including patients with a history of pelvic surgery, obvious bladder overactivity, benign prostatic hyperplasia, urethral stricture, pelvic organ prolapse, urological malignancy, and neurogenic bladder, as well as patients with end-stage renal disease or acute urinary tract infection. The main outcome was daily salt intake estimated by calculating sodium and creatinine concentrations of spot urine samples. Lower urinary tract symptoms were measured by the core lower urinary tract symptom score (CLSS) questionnaire, and average urinary volume and frequency was evaluated using a three-day frequency volume chart. Subjects included 728 participants (229 men and 499 women). Subjects were divided into a low salt intake group (L-salt group) and a high salt intake group (H-salt group) based on the median salt intake. Subjects in the L-salt group ingested < 9.2 g/day and subjects in the H-salt group ingested > 9.2 g/day. Subjects in the H-salt group were older, had higher body mass index, and were more likely to be hypertensive, but were less likely to have hyperlipidemia. Daytime and nighttime frequency, as well as diurnal and nocturnal urine volumes as measured by voiding charts, were significantly higher in the H-salt group

compared to the L-salt group and were correlated with daily salt intake. Daytime frequency and nocturia as measured by CLSS were significantly higher in the H-salt group. On multivariate analyses, salt intake and hypertension were independent factors for the daytime frequency and nocturia.

## ■ COMMENTARY

Hashim et al summarized International Continence Society (ICS) recommendations on nocturia and reviewed definitions and guidelines regarding the evaluation of nocturia. The symptom of nocturia refers to a patient's report of waking at night to pass urine. The sign of nocturia is indicated by the number of times a person awakens.

In reading the recommendations, I was intrigued by the authors' brief summary of urine production and output volume. The ICS recommendations outlined that urine production rates increase when the following conditions exist: diuresis, natriuresis, conditions in which large quantities of products are present in the glomerular filtrate (such as poorly controlled diabetes mellitus), or renal tubule dysfunction.[1] Although my own evaluation of patients with frequency and nocturia frequently involves considerations of diuresis, fluid intake, glucosuria, or diabetic control as well as renal function, it rarely has focused on natriuresis. Natriuresis is the process of sodium excretion in the urine. Surplus salt increases sodium excretion and urine production.

To date, little data exist on the relationship between salt intake, urinary frequency, and nocturia. The study by Matsuo et al is one of the first reporting a positive relationship. The Centers for Disease Control and Prevention's 2015-2020 Dietary Guidelines for Americans recommend that Americans consume < 2,300 mg of sodium daily and state that, on average, most Americans consume at least 3,400 mg each day.[2] Sodium can add up quickly, since many foods, especially processed foods such as canned goods, salad dressings, deli meats, and snacks, contribute to high amounts of sodium. Interestingly in this study, the estimated daily sodium intake was 9,200 mg daily, with the median intake 7,400 mg in the L-salt group and 11,400 mg in the H-salt group. Unlike prior studies, Matsuo et al did not rely on self-report to determine salt intake but instead used a validated calculation of salt intake based on spot urine samples. It is unclear whether U.S. estimates of salt consumption are accurate or whether the relationships found in this study hold true in patients with lower salt intake. This study was limited in being able to fully explain the relationships between voiding and salt intake. Numerous confounding factors may affect these relationships, including the relationship between hypertension and salt intake, medical comorbidities (including sleep apnea, congestive heart failure, lower extremity edema), sleep quality, and diuretic use. In addition, the authors did not collect data regarding type and quantity of fluid consumption.

The ICS recommendations regarding nocturia center around identifying patients' symptoms and distinguishing these from bother, as well as evaluating signs of nocturia by physical examination (including post-void residual) and bladder diary. Together, these allow the distinction between 24-hour polyuria, which can result from diabetes, diabetes insipidus, or salt loss; nocturnal polyuria aggravated by sleep apnea and peripheral edema; lower urinary tract dysfunction; or sleep disturbance. Although additional studies are needed to determine the complex relationships between salt intake and daytime and nighttime voiding, when evaluating urinary frequency and nocturia, we might consider inquiring about our patients' salt consumption alongside their fluid intake, medications, and medical comorbidities. ■

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SPECIAL FEATURE

# Expedited Partner Therapy: We Can Do More


***By Rebecca H. Allen, MD, MPH***

*Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI*


**Dr. Allen reports she is a Nexplanon trainer for Merck.**

Expedited partner therapy (EPT) is defined as treating the heterosexual partners of patients diagnosed with chlamydia or gonorrhea by providing the medication or a prescription for the patient to give to the partner without a healthcare provider first examining the partner.[1] EPT is endorsed by the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Family Physicians, the American Academy of Pediatrics, the American Bar Association, and the Society for Adolescent Health and Medicine. Although referral of the partner for a full sexual health examination is preferred, often there

**Table 1: Legal Status of Expedited Partner Therapy in the United States[1]**

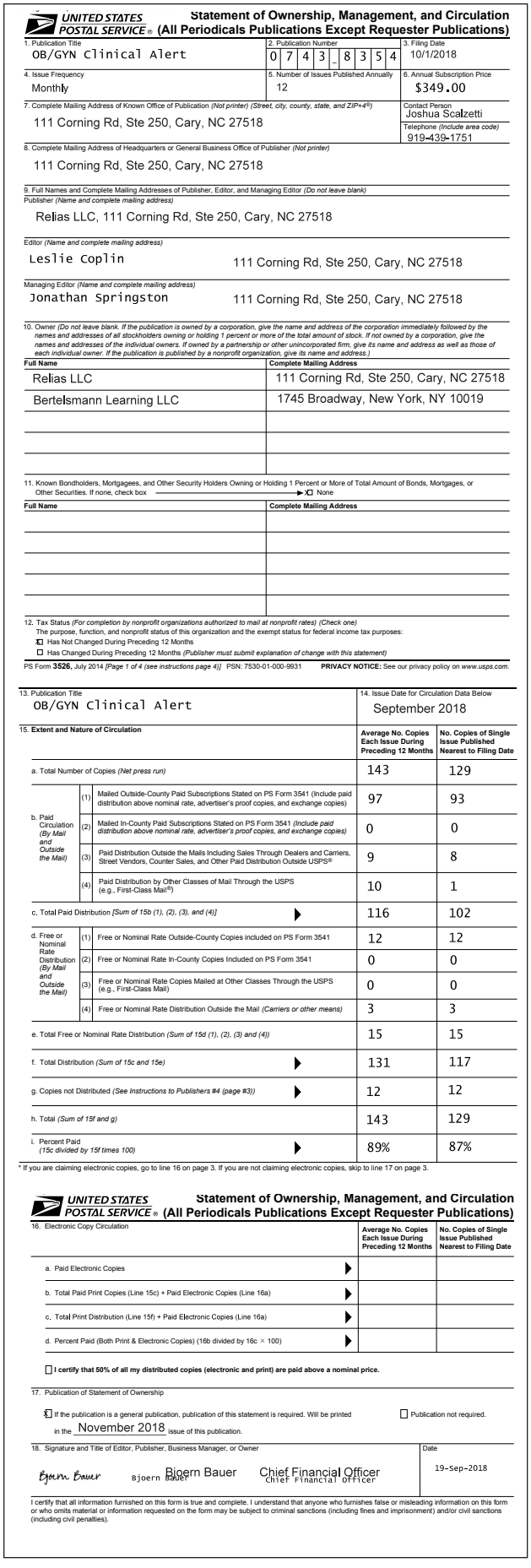
| Prohibited | Potentially Allowable |
|---|---|
| • Kentucky<br>• South Carolina | • Alabama<br>• Delaware<br>• Kansas<br>• New Jersey<br>• Oklahoma<br>• Puerto Rico<br>• South Dakota |
| **Remainder of states: Permissible** | |

are barriers for partners to receive treatment, such as cost, lack of health insurance, or no established relationship with a physician. EPT offers an alternative to ensure that the partner receives treatment and does not re-infect the index patient. EPT is legal in 42 states and potentially allowable in six states and one territory.[1] (*See Table 1.*) Of note, EPT is not yet recommended for the management of sexually transmitted infections (STIs) in men who have sex with men because of the concern of missing STI and HIV coinfections in this population.[2]

Renewed focus has been placed on EPT as STI rates have soared recently in the United States. In 2016, there were 1.6 million cases of chlamydia, 470,000 cases of gonorrhea, and almost 28,000 cases of primary and secondary syphilis.[3] This was the highest number of chlamydia cases ever reported to the CDC.[4]

This increase in cases is attributable partially to the decreased funding of the U.S. public health infrastructure. State health departments are underfunded and many have had to decrease their direct clinical services that offer STI testing and treatment.[5] In my own state of Rhode Island, the only free and confidential state-funded STI clinic was closed because of budget cuts in 2011. Untreated STIs particularly are harmful to women, as they can lead to pelvic inflammatory disease, chronic pelvic pain, and infertility. Adolescent and young women between 15 and 24 years of age accounted for 46% of the reported chlamydia cases in 2016. Therefore, any OB/GYN provider plays a direct role in combatting this epidemic with screening, treatment, and EPT. ACOG recommendations cover the following aspects of EPT implementation.[6]

- Offer EPT to a patient's recent sexual partners who are unable or unlikely to access medical services. Specifically, the offer includes a patient's last sexual partner and any within the previous two months.
- Provide patient counseling and written instructions for the partners offered EPT.
- Provide encouragement for the partners to seek additional medical evaluation, including testing and treatment for HIV infection and other STIs.
- Instruct patients to abstain from intercourse for seven days after treatment is complete for them and their partners.
- When considering EPT, assess the risk of intimate partner violence associated with STI notification.



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- Do not offer EPT in cases of suspected child abuse or sexual assault.

For OB/GYN providers, implementing EPT is simplest for women diagnosed with chlamydia infection. A prescription for 1 gram of azithromycin can be written easily for their male partner with instructions to the pharmacist to screen for allergies. However, for women diagnosed with gonorrhea infection, the situation is a little more complicated. As of 2012, the CDC no longer recommended oral cefixime for the treatment of gonorrhea. Currently, the only CDC-recommended treatment of gonorrhea is combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus a single dose of azithromycin 1 gram orally. Since intramuscular injections are not used in EPT, the CDC has stated that "if a provider considers it unlikely that a heterosexual partner of a gonorrhea patient will access timely evaluation and treatment, EPT with cefixime and azithromycin still should be considered, as not treating partner(s) is significantly more harmful than is the use of EPT for gonorrhea."[7]

Clearly, more work needs to be done to implement EPT in our clinical practices. Barriers to EPT include the stigma surrounding STIs, patients being unaware of EPT or not feeling comfortable contacting their partners, the cost of prescriptions for EPT, and providers not offering EPT.[4] Certainly, more providers need to be trained on the legality, safety, effectiveness, and implementation of EPT. Electronic medical record reminders also could serve as a useful tool in this area, and the cooperation of pharmacists is critical. Let's try to make EPT a routine part of clinical care for our patients to halt the wave of chlamydia and gonorrhea infections currently inundating the country. ■

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## CME/CE QUESTIONS

1. **Infertile women who become pregnant, regardless of treatment, have increased odds of cesarean delivery compared to normal fertile women.**
   a. True
   b. False
2. **Compared to normal-weight girls of the same age, the risk of adult infertility is:**
   a. increased three-fold among girls with obesity at age < 12 years
   b. increased three-fold among girls with obesity at age > 12 years.
   c. reduced two-fold among underweight girls < 12 years.
   d. reduced two-fold among underweight girls > 12 years.
3. **Which of the following statements is true based on results from the study on salt intake by Matsuo et al?**
   a. Subjects with high salt intake are healthier.
   b. Higher salt intake is associated with increased daytime and nighttime frequency.
   c. Hypertension is not associated with urinary frequency.
   d. Subjects with higher salt intake have fewer lower urinary tract symptoms.