ABSTRACT & COMMENTARY

Antral Follicle Count Does Not Predict Pregnancy During Unstimulated Donor Insemination Cycles

By Michael A. Thomas, MD

When couples or single women present to our offices with difficulty achieving pregnancy, we do everything we can — obtain a history, a thorough physical examination, limited laboratory testing, and imaging — to get an accurate picture of their chances of achieving pregnancy. If there is a male partner, it becomes somewhat easy to rule in or rule out a problem in the semen by obtaining a semen analysis. In contrast, evaluation of female infertility requires the clinician to address multiple factors, including ovulation potential, tubal patency, uterine cavity architecture, and hormonal issues. As part of the standard workup, healthcare providers increasingly rely on the use of ovarian reserve testing to assess the “number of eggs that are remaining.” Tests commonly used include either antral follicle count (AFC; transvaginal ultrasound assessment of antral follicles present in the early follicular phase), serum follicle-stimulating hormone (FSH; assessed on cycle day 3), or a serum anti-Müllerian hormone (AMH; assessed at any time during the menstrual cycle). Each of these has its merits and they often are used in combination.

With this in mind, investigators from Canada performed a retrospective cohort analysis of 459 eumenorrheic women who underwent 1107 unstimulated donor insemination cycles over 7 years. These women did not have a diagnosis...
of infertility, had a normal uterine cavity with patent tubes, and were either single, in a same-sex relationship, or had a partner with a severe male factor. All couples used cryopreserved sperm from a commercial sperm bank. Timing of insemination was performed using a urine luteinizing hormone (LH) surge test or by monitoring daily serum LH levels. AMH was not routinely used in their center and, therefore, was not measured in the study. All women underwent an AFC in the early follicular phase (cycle day 2-4). During this process, transvaginal ultrason was used to count the number of follicles in both ovaries measuring 2-9 mm. A low AFC was determined to be 0-12 follicles, medium AFC 13-23 follicles, and high AFC ≥ 24 follicles. The age range was 23-46 years, and subjects were divided into three different age groups: ≤ 35 years of age (Group 1), 36-39 years of age (Group 2), and ≥ 40 years of age (Group 3). Participants were observed up to three cycles and a cumulative pregnancy rate was calculated.

Clinical pregnancy was defined as a fetus with a heartbeat between 6-8 weeks. Miscarriage was defined as a positive hCG and no fetal heartbeat noted up to 10 weeks’ gestation. A total of 127 pregnancies was observed, with an overall clinical pregnancy rate of 12.46% and a multiple rate of 1.6%. Twenty of the 127 pregnancies resulted in miscarriage (13.61%). Pregnancy rates were noted to decline with increasing maternal age. However, within the same age group, the pregnancy rate was not different whether the AFC was low, medium, or high. Even when a secondary analysis was done where the AFC was further subdivided between very low, low, medium, and high, no difference in pregnancy rate was noted. Although miscarriage rates increased with increasing age, no differences were noted within age groups when AFC was analyzed.

## COMMENTARY

Since most healthcare plans fail to cover fertility care, cost is an important factor to discuss with any woman/couple pursuing fertility treatments. Most of these treatment protocols include the use of clomiphene citrate, letrozole, and/or injectable gonadotropins with timed intercourse, insemination, or in vitro fertilization. This all amounts to costs ranging from hundreds to thousands of dollars. Since nearly all couples have failed to achieve pregnancy with natural or unstimulated cycles, this current Canadian trial may not be applicable to the usual couple pursuing fertility treatment in America.

In this country, neither patients nor health professionals have the time, financial resources, or patience to undergo three full cycles without some type of intervention. Couples are distraught, expectations run high, and fertility practices compete vigorously for patients. Practices advertise their expertise (and higher-than-imaginable pregnancy rates) via social media, television ads, and carrier pigeon.

However, this study demonstrates that the majority of eumenorrheic women with normal uterine and open tubes who only need donor sperm really do not need the million-dollar workup. The use of ovarian reserve testing to predict the number of eggs still available is unnecessary. According to the latest guidelines by the Practice Committee of the American Society of Reproductive Medicine and a previous publication, all of the commonly used ovarian reserve tests available (day 3 FSH, AMH, or AFC) primarily help to predict how well someone will respond to ovulation induction medications rather than specifically predicting pregnancy outcomes. The Ripley study reviewed here provides additional evidence that ovarian reserve testing does not benefit women with normal cycles.

In essence, results from this study demonstrate that ovarian reserve testing is not a crystal ball to predict future pregnancy. This is an important clinical pearl. Although an older nulliparous woman may hope to gain confidence from ovarian reserve testing, it’s important to realize the clinical applicability of these tests. What you really do is counsel that fertility first begins with ovulatory cycles, a normal uterus, open tubes, and sperm. As we have known for many years, up to 85% of women younger than 35 years of age who are regularly exposed to sperm over 12 months will get pregnant.1 We continue to have a population explosion around the world due to this fact alone. The fertility process has been highly commercialized, and the Internet has exploded with numerous websites by trained and untrained “experts” who prey on the fears of people who may not actually have a problem. Therefore, it is difficult for American women to figure out who to trust when they have difficulty conceiving. The best bet for the majority of women may be regular timed intercourse with normal sperm (from a partner or donated) — no medications, no injections, and no testing, just reassurance and education from a healthcare provider who has her best interest at heart.

## REFERENCES

ABSTRACT & COMMENTARY

Non-medically Indicated Inductions of Labor

By John C. Hobbins, MD

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

SYNOPSIS: A recent study in patients having non-medically indicated inductions of labor has shown that this option is associated with higher cesarean section rate at 38 and 40 weeks, but not, interestingly, at 39 weeks, at which time there was a lower rate of peripartum infections, fewer newborn special care unit admissions, but longer labors. However, these data do not speak for empiric induction of labor at 39 weeks without medical indication.


Inductions of labor (IOL) alarmingly increased from 2% in 1991 to 8% in 2006.1 Then, in another upward swing, a 2009 ACOG Practice Bulletin stated that 22% of all deliveries in the United States were linked with IOL.2 During that same time frame, there had been a concomitant rise in the cesarean section rate (CSR) with, at last count, a rate of 32.8%.3 One would expect a direct relationship between the two trends in medically indicated IOLs since the reason alone for the inductions would predispose those patients to a higher CSR, but it is unclear how much non-medically indicated IOLs affect the CSR.

For good reason, there has been a move on the part of official medical bodies and many individual hospitals to discourage elective cesarean section in early-term patients (at < 39 weeks), since studies have shown a higher rate of neonatal morbidity at this time compared with ≥ 39 weeks.4 In an attempt to see if this trend is the same for elective inductions, authors from the Maternal-Fetal Medicine Units (MFMU) network evaluated, by secondary analysis, 31,169 patients in 25 centers over a 3-year period (2008-2011).5 They compared neonatal outcomes of those babies delivered between 38 and 41 weeks by non-medical IOL and those in whom no intervention was attempted (“expectant management”).

At 39 weeks they found no difference in composite neonatal adverse outcomes, but there was a lower rate of admissions to the NICU (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.47-0.93) and maternal peripartum infection (OR, 0.66; 95% CI, 0.49-0.86) with non-medically indicated IOL vs expectant management. At 39 weeks there was no statistically significant difference in CSR (25.8% vs 23.8% with an OR of 1.13; 95% CI, 0.94-1.36). However, those patients with non-medically indicated IOL spent 3 hours longer in the hospital between admission and delivery. If inductions were attempted at 38 weeks or 40 weeks, the CSR was significantly higher with an OR of 1.50 (95% CI, 1.15-1.46), respectively.

COMMENTARY

The results show that inductions for non-medical reasons between 39 and 41 weeks resulted in modest or no neonatal benefit, a lower rate of peripartum infection, but an increase in CSR at 38 and 40 weeks.

It is important to emphasize that the data in the MFMU study again endorse the admonition to hold off delivering early-term babies electively without an indication in view of the 50% increase in the CSR without neonatal benefit at 38 weeks. Although suggesting a possible maternal benefit to IOL at 39 weeks, the results in no way represent a “license to induce” all patients at this time. Why?

1. As pointed out in the companion editorial by Caughey,6 expectant management includes patients who can develop problems later in pregnancy, such as preeclampsia, intrauterine growth restriction, glucose intolerance, and even later, post-term pregnancy. The analysis did not compare non-medically indicated IOL with spontaneous labor at the same gestational age. In effect, the benefit of a pre-emptive (and non-physiologic) strike at 39 weeks in uncomplicated patients might only be to protect normal fetuses from completely unexpected events to come.

2. This was a retrospective analysis and not a randomized clinical trial, which would better test the hypothesis.

3. Since cost containment is a factor in today’s delivery of care, another study did not find IOL at 39 weeks to be cost-effective,7 and this did not include the extra 3 hours in the hospital noted in the MFMU study.

At 41 weeks, studies have found IOL to be efficacious and cost-effective.8 However, induction decisions (without medical indication) in the window between 39 and 41 weeks should await further study.

REFERENCES

ABSTRACT & COMMENTARY

Liletta: A New LNG-IUS Option

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: Initial clinical results with a new 52 mg levonorgestrel intrauterine system (LNG-IUS) recently introduced to the market and approved for 3 years of use are similar to those seen with the existing LNG-IUS.


A new 52 mg levonorgestrel intrauterine system (LNG-IUS) was evaluated in an open-label, Phase 3 study conducted at 29 clinical sites in the United States. The device uses the same 32 mm x 32 mm T frame as the existing LNG-IUS, and a similar release rate-controlling membrane over the drug reservoir on the stem of the device designed to deliver 20 mcg/day of LNG.

A total of 1600 women aged 16-35 years and 151 women aged 36-45 years underwent attempted placement of the new LNG-IUS in the study. Of these, 1011 (57.7%) were nulliparous and 438 (25.1%) were obese women. Up to two placement attempts were allowed, and successful placement occurred in 1714 out of 1751 (97.9%) women. Of the 37 failed placements, 15 did not undergo an attempt at IUS insertion due to failed cervical dilation, a small uterine cavity, or other reasons unrelated to the product.

Subjects were seen at 1, 3, and 6 months after IUS placement, and then followed every 6 months. All subjects were required to be sexually active with a male partner and at risk for pregnancy. Subjects kept a diary of symptoms and sexual activity.

A total of six pregnancies occurred during the 3-year study for a cumulative life-table pregnancy rate of 0.55 (95% confidence interval [CI], 0.24-1.23); the Pearl Index for the 34,711 women-cycles of LNG-IUS use in the efficacy cohort of women ages 16-35 was 0.15 (95% CI, 0.02-0.55) through year 1, 0.26 (95% CI, 0.10-0.57) through year 2, and 0.22 (95% CI, 0.08-0.49) through year 3. Of the six pregnancies, four were ectopic. By the end of 3 years of use, 39% of subjects aged 16-35 and 32% aged 36-45 discontinued study participation. The most frequent reasons for discontinuation were adverse event (12%), lost to follow-up/withdrawal of consent (8%), and desire for pregnancy (5.5%). Of note, among those women who discontinued to become pregnant, 87% conceived within 12 months. The expulsion rate was 3.5%, and most (81%) of these occurred during the first year of use.

COMMENTARY

A new LNG-IUS (Liletta™) was approved in the United States in February and will be marketed by Actavis. The device is manufactured in Belgium, and the clinical trial to bring the device to the United States was conducted by Medicines360, a company that describes itself as a non-profit women’s health pharmaceutical company. The clinical trial was made possible through generous funding from an anonymous foundation. While it is tempting to consider this a “generic” version of Bayer Healthcare’s Mirena™, it is important to note that no regulatory pathway exists for approval of a generic drug-releasing device. Therefore, a clinical trial was required to bring this product to market.

While not a generic, Liletta (the new device) shows a remarkable resemblance to Mirena (the existing device). Both use the same 32 x 32 mm Nova-T plastic frame, and position a 52 mg reservoir of levonorgestrel on the stem of the device. Both utilize a rate-controlling membrane to titrate release of the hormone. From the package insert, the initial release rate is listed at 20 mcg/day for the existing IUS and 18.6 mcg/d for the new product. The release gradually decreases over time for both devices. Given that the release rates are essentially the same, the clinical performance for the new device would be expected to be the same as the existing device.

Important differences do exist, but most of these will impact clinicians and not patients. The most important will be noticeable when you open the box of the new device. Compared to the well-engineered insertion device of the existing 52 mg LNG-IUS, the insertion device of the new IUS appears somewhat crude. This is not surprising given that Bayer has spent more than 20 years improving its insertion system and has tied up a number of important patents on the mechanism of insertion devices along the way. But even though the insertion process of the new system is not as fluid as with the existing device, the clinical performance appears to be the same; the failed placement rate of 2% is similar to that seen with the existing IUS. The removal threads are blue, compared to the brown removal
threads of the existing device. Practically speaking, both appear dark or black when seen protruding through the cervix. The ultrasound appearance will also be the same, so it will be difficult to tell the two devices apart on a clinical exam.

Although a head-to-head comparison was not done, the clinical performance of the new system over 3 years is virtually identical to that of the existing device. One important difference is that more than half of the women who participated in the clinical trial of the new device were nulliparous. Thus, this study provides additional safety information about the use of the LNG-IUS in this important (and growing) group of users. Clinical sites provided same-day insertion, collecting tests for chlamydia at the time of placement with no delay for results (those screening positive received treatment without removing the IUS).

This provides another important pearl; of the 23 of 1751 (1.3%) subjects who tested positive for chlamydia at the time of IUS placement, none developed a pelvic infection. Only three subjects (0.2%) underwent premature removal for pelvic infection during the course of the study. The most important consideration for patients is that the device has initial labeling for only 3 years of use. However, 5-year efficacy data are currently being analyzed for Liletta™, and a cohort of subjects from the pivotal trial will continue for an additional 2 years to obtain data in support of approval for 7 years of use for contraception. As these data become available, the labeling will be modified. Another important point is that unlike the existing IUS, the new product does not have FDA approval for treatment of heavy menstrual bleeding.

So if this new product is not different from the existing IUS, why was it developed? The major concern with the existing LNG-IUS has been high cost, not clinical performance, as cost presents a barrier to access. It is expected that the price for the new LNG-IUS will be substantially lower than the existing IUS, at least in publicly funded clinics. It is likely that private clinics and health plans will also enjoy a price reduction due to competition between the existing and new product. Having another hormone-releasing IUS on the U.S. market is a good thing and should expand options for women. But this is only a start. We can also look forward to additional copper devices coming to the U.S. market in the next few years. ■

REFERENCE

ABSTRACT & COMMENTARY

Why Aren’t Women Using Contraception?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck, a Liletta trainer for Actavis, and on the advisory board for Bayer, Actavis, and Vermillion.

SYNOPSIS: This cross-sectional study highlights new risk factors for nonuse of contraception among women at risk for unintended pregnancy: women within 12 months of their first episode of sexual intercourse, women who perceive themselves to be infertile, and women who are cohabiting but not married.


This is a cross-sectional study using data from the combined 2002 and 2006-2010 National Surveys of Family Growth (NSFG), a national sample of 19,922 women of reproductive age. The first part of the study analyzed interviews with 9675 sexually active women at risk of an unintended pregnancy, including women who were using contraception (except sterilization) and those who were not. Women (n = 10,247) who were currently pregnant, trying to become pregnant, 6 or fewer weeks postpartum, or sterilized were excluded from the study. Analysis variables included age, race, relationship status, parity, education, income, and time since cotarche.

Fecundity status as reported by the woman was also included. Women were considered to have impaired fecundity if they reported that it was physically difficult or impossible for her to become pregnant or for her partner to father a child. Logistic regression was used to evaluate the multivariate predictors of nonuse of contraception among women at risk of an unintended pregnancy. The second part of the study consisted of data from 990 women who had an unintended birth in the 3 years before the interview and were not using contraception in the month prior to the pregnancy. Whether or not the pregnancy was intended was measured as intended, unwanted, mistimed less than 2 years, or mistimed 2 years or more.

The authors found that among the 9675 women interviewed, 16.5% were not using contraception. Nonuse of contraception was correlated with extremes of age (adolescents and those age 35 years and older), being unmarried even if cohabitating, and both foreign-born and U.S.-born black women. Nulliparous women within 12
months of their first episode of sexual intercourse were more likely to be contraceptive nonusers than nulliparous women who had been having sex for more than a year (22% vs 15%, P < 0.01). Women who reported impaired fecundity also were more likely to not use contraception than women who reported normal fecundity (30% vs 15%, P < 0.001). Multiple logistic regressions confirmed these findings while controlling for age, race, education, insurance coverage, fecundity, and time since first sex. In the second part of the study, the reasons women gave for nonuse of contraception that led to their unintended pregnancy in the 3 years before the interview were: 41% said they “did not think I could get pregnant,” 24% said they “did not expect to have sex,” 20% said they “didn’t really mind getting pregnant,” 12% said that their male partner didn’t want her to use birth control or he didn’t want to use birth control himself, and 10% were “worried about the side effects of birth control.”

**COMMENTARY**

With the unintended pregnancy rate in the United States hovering around 50% for decades, it is important for us to understand reasons women at risk of unintended pregnancy are not using contraception. Although previous studies have found that younger age, unmarried relationship status, black race, and lower education levels are associated with nonuse of contraception, this study aimed to expand the knowledge of risk factors for nonuse of contraception and to explore exactly why women were not using contraceptives before an unintended pregnancy. The strength of this study was a large national sample that is representative of the U.S. population. This study confirmed previous findings and also highlighted some newer risk factors.

First, even controlling for age, nulliparous women within 12 months of their first episode of sexual intercourse were 1.6 times as likely to not use contraception compared to nulliparous women who had been having sex for longer. This implies that women new to sexual activity are less able or inclined to access contraception, perhaps due to lack of experience or knowledge. It is important, then, that even when women report that they have never been sexually active, clinicians should counsel them about contraception and their reproductive life plan.

Second, while it was known that women who had never been married were at risk for nonuse of contraception compared to married women, this study points out that cohabitating women also have a higher odds for nonuse (odds ratio = 2.3) compared to married women, even after controlling for age and other variables. Since it is known that cohabiting women have much higher unintended pregnancy rates than other marital status groups, this may be partly due to nonuse of contraception. The reason for this disparity is not known but is concerning given that marriage rates are declining nationally.

Third, and perhaps most importantly, approximately 14% of the sample reported that they had impaired fecundity. These women were 2.5 times more likely to be nonusers of contraception than women who reported no fecundity impairments. While this may make sense from the woman’s perspective, it is unclear why they thought they could not get pregnant, e.g., this was self-report, not a medical diagnosis. In addition, the most common reason cited for not using contraception prior to an unintended pregnancy and birth in this study was “I did not think I could get pregnant.” Unfortunately, this study does not allow us to know why women thought that they were infertile. This is an area of important research that has also been investigated by social scientists at the University of California San Francisco (UCSF). They have performed some fascinating studies on why women have unprotected intercourse even though they do not want to get pregnant. Indeed, they have shown that women often have misconceptions about the chances of conception and the effectiveness of contraception. In studies of almost 2000 women at 13 family planning clinics across the country, UCSF researchers found that the most common categories of reasons women cited for having unprotected sex in the past 3 months were: barriers accessing birth control, not planning to have sex, and infertility beliefs. The most commons specific reasons were: “I did not think I was going to have sex,” “I ran out of the birth control method I was using,” and “I did not think I could get pregnant because I had had unprotected sex before without getting pregnant.” The researchers found that women who had unprotected intercourse tended to overestimate the risk of pregnancy from a single act of intercourse and conversely underestimate the risk of pregnancy from 1 year of unprotected intercourse. Women were also found to underestimate the protective benefits of contraception. The authors concluded from their data that women don’t really understand the risk they are taking by having cumulative episodes of unprotected sex.

I am not surprised by these findings because I often encounter women who have doubts about their fertility if they have unprotected sex for a while and do not conceive. I think these women have a false sense of security that they cannot get pregnant. While I would like to blame this on the lack of comprehensive sex education in our country, I have to admit that we also need to do a better job of educating our patients. After all, why would women use contraception consistently and correctly if they doubt either that it works or that it is needed for every single act of intercourse? We need to improve women’s understanding of the risk of conception when having unprotected sex and of the protective effects of using long-acting reversible contraceptives.

**REFERENCES**

Progress in Obstetrics and Gynecology

Progesterone and Indomethacin and PTL

By John C. Hobbins, MD

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

SYNOPSIS: One recent study has questioned the efficacy of the ability of 17 alpha-hydroxyprogesterone caproate to prevent preterm birth, and the other suggests that indomethacin, used to stop preterm labor, may have unwanted neonatal consequences.


There were no significant differences in respiratory distress syndrome, patent ductus, neonatal sepsis, bronchopulmonary dysplasia, or total amounts of intraventricular hemorrhage (IVH) (all grades). However, there were increased rates of severe IVH (grade 3 and 4) (relative risk [RR], 1.29; 95% confidence interval [CI], 1.06-1.56), necrotizing enterocolitis (RR, 1.36; 95% CI, 1.08-1.71), and periventricular leukomalacia (RR, 1.59; 95% CI, 1.17-2.18) in women given indomethacin compared to controls. The authors concluded that the use of indomethacin “should be avoided.”

COMMENTARY

It has been 12 years since Meis et al published the seminal study showing a decrease in the rate of PTB by 40% in patients with a history of prior PTB who were prescribed 17P. Since then, weekly injections of 17P have been a part of the lives of, seemingly, most patients with a history of a prior delivery at less than 37 weeks. Along the way, the finding of a short cervix also began playing a role in strategies to prevent PTB. In fact, a 2011 study by Hassan et al showed that progesterone halved the rate of PTB <37 weeks and decreased the rate of respiratory distress syndrome when a natural progesterone product was inserted daily into the vagina. This study had a mixture of high- and low-risk patients. Very recently, there has been a suggestion that even in low-risk patients with short cervices, this regimen can be cost-effective. Although it is tempting to surmise that all progesterones are the same, no matter how they are applied, thoughtful physicians have been in a quandary as to which product to use in various situations. Now the above study casts some doubt as to whether 17P works at all in those with short cervices and a history of predisposing factors — the very patients who are at greatest risk. However, before abandoning 17P, it should be stated that this study has its own set of problems, including the possible confounding factors of cerclage and the small numbers in the study. Interestingly, the percentage of patients who delivered preterm in the study (45%) is far greater than other RCTs involving PTB. This was particularly surprising since this high-risk group of study patients represented a heterogeneous group, which included some with only a history of cervical surgery (such as LEEP procedures) whose risk of PTB is still relatively low. Also, importantly, before immediately switching over to vaginal progesterone (based on this one 17P study), this vaginal delivery method still needs more study.
needs to stand up to further scrutiny. Regarding indomethacin, there have been a few older studies suggesting its efficacy in stopping preterm labor, but the greatest concern has always been its possible ability to prematurely close the fetal ductus arteriosus. This concern has caused us to avoid its use during a critical time (28-32 weeks) when the ductus is most vulnerable to this effect. In fact, we have mostly been using it to diminish uterine activity after placing a cerclage, since its mechanism of action (prostaglandin synthetase inhibition) suits a situation where surgical trauma to the cervix can theoretically increase prostaglandin release.

This study also is far from pristine. Since there were not enough useful data in the literature regarding randomized clinical trials, the authors had to use pooled data from observational studies. These studies, as the authors later pointed out, are “inherently more prone to bias.” Also, it was impossible to tease out which patients were exposed to other tocolytics at the same time, and the indomethacin might have been used as a “last-ditch” effort in pregnancies most prone to neonatal problems. Last, with this type of pooled data, any result with an RR < 2.0 must be interpreted with caution since meta-analyses are truly a mixed bag covering a wide range of confidence intervals. To quote Leon Speroff (the past chief editor of OB/GYN Clinical Alert), “To combine a large number of studies into one large pooled analysis is not bringing together a bunch of apples to make a Big Apple, but simply mixing fruits to make a fruit salad.”

REFERENCES


CME QUESTIONS

1. Which of the following is a recognized test of ovarian reserve?
   a. Midluteal progesterone
   b. Inhibin C
   c. Anti-Müllerian hormone
   d. Early follicular testosterone

2. At which gestational age has elective induction of labor been shown to be beneficial and cost-effective?
   a. 39 weeks
   b. 40 weeks
   c. 41 weeks
   d. Never

3. Compared to the existing LNG-IUS, the results of the Eisenberg study with a new 52 mg LNG-IUS show clinical performance that has:
   a. similar contraceptive and safety profile to the existing LNG IUS at 3 years of use.
   b. a similar effect on heavy menstrual bleeding as the existing LNG IUS.
   c. both similar contraceptive effect and bleeding effects as the existing LNG IUS.
   d. similar contraceptive effects but more side effects than the existing LNG IUS.

4. Which is not associated with the nonuse of contraception?
   a. Age less than 20 years
   b. Being married
   c. Being newly sexually active
   d. Believing yourself to be infertile

5. According to a recent meta-analysis, indomethacin had its greatest effect on which of the following?
   a. Periventricular leukomalacia
   b. Neonatal sepsis
   c. Patent ductus
   d. Bronchopulmonary dysplasia

[IN FUTURE ISSUES]