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INSIDE

Perinatal Mortality and Assisted Reproductive Technologies: A Meta-Analysis

ABSTRACT & COMMENTARY

SOME EUROPEAN STUDIES INDICATE THAT 2-3% OF PREGNANCIES occur through assisted reproductive techniques (ART) while US statistics suggest that about 0.9% of all pregnancies result from ART. Although there has been much written about the profusion of multiple gestations secondary to ART, little attention has been directed toward singleton pregnancies. However, very recently an article appeared by Jackson and colleagues that explored the relationship between ART and adverse pregnancy outcomes in singleton pregnancies.

The group searched the literature for studies dealing with ART in singleton pregnancies and out of 1400 studies found since 1978, only 15 satisfied Jackson et al's rigid criteria for analysis. ART pregnancies consisted of ovulation induction, egg retrieval, and in vitro fertilization (IVF) with intrauterine transfer of fresh embryos. These pregnancies were compared with singletons that were conceived spontaneously and, most importantly, were matched according to parity and maternal age.

They found a statistically significant increase in the ART group with regard to perinatal mortality (OR, 2.2; 95% CI, 1.6-3.0), preterm delivery (OR, 2.0; 95% CI, 1.7-2.2), low birth weight (OR, 1.8; 95% CI, 1.4-2.2), and very low birth weight, defined as below 1500 grams, (OR, 2.7; 95% CI, 2.3-3.1). Last, they found an increase in SGA of 1.6 (95% CI, 1.3-2.0).

COMMENT BY JOHN C. HOBBINS, MD

In previous *OB/GYN Clinical Alert*s, we have touched upon the incredible rise in multiple gestations from ART and its public health effect. For example, the rate of twins has risen from 1 in 80 to 1 in 40 over the last few years. According to the CDC, in 2001, the incidence of multiple births after ART was 42% for fresh donor eggs and 36% for insemination of the patient's eggs. In some states more than 60% of live births from ART were multiple gestations. According to a 1995 NIH registry, multiple births contribute 22% of very low birth weight babies to neonatal intensive care units (NICU's) and half of these result

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from ART. Also, as pointed out before in another *OB/GYN Clinical Alert*, twins are 6 times more expensive to manage than singletons from the beginning of pregnancy to neonatal discharge. Triplets are 11 times more expensive.

Now we find that singletons conceived through IVF have, on average, a 2-fold greater chance of dying, of being born preterm or very preterm, and of being small-for-gestational age (SGA).

So, what is going on here? Is the adverse pregnancy outcome related to the treatment itself or an inherent predisposition towards these problems in patients requiring specialized fertility help? One recent study showed that, when compared with spontaneously conceived singleton pregnancies, there was a 50% increase in preterm birth with "low tech" methods (intrauterine insemination) and a 2-fold increase in preterm birth with the "high tech" IVF. Others have found that seemingly infertile patients conceiving without treatment had a higher rate of perinatal loss and delivered very low birth weight singletons more frequently than those who had no fertility problems.

Putting this together, patients experiencing trouble conceiving without treatment have an increasingly higher rate of adverse pregnancy outcome to start with, and the more complicated the treatment to get these patients pregnant, the greater the risk of fetal mortality and morbidity.

Interestingly, the above meta-analysis from Jackson et al indicated more inductions of labor and Cesarean sections were done in the ART pregnancies. They felt that these "special" pregnancies might be more subject to maternal pressure and provider intervention, "thus leading to iatrogenic preterm delivery and low birth weight." However, this would not account for the increase in very low birth weight, perinatal mortality or SGA.

Women having trouble conceiving may not sail blithely through pregnancy without adversity, and it is unclear whether it is the environment into which these embryos alight, or the ends to which these patients will go to conceive, that are the responsible factors. Whatever the cause, each patient should be properly apprised of the results of this study, as well as of the data on twins, before entering infertility treatment. ■

Suggested Reading

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Endometrial Biopsy Using Intrauterine Lidocaine Plus Naproxen Sodium

ABSTRACT AND COMMENTARY

Synopsis: *Endometrial biopsies were performed using intrauterine lidocaine only, naproxen only, both, or neither. Intrauterine lidocaine significantly reduced the pain when used in conjunction with oral naproxen sodium.*

Source: Dogan E, et al. *Obstet Gynecol*. 2004;103: 347-351.

In this randomized, double-blind, placebo-controlled trial, patients undergoing Pipelle endometrial

biopsy were assigned to one of 4 groups of 30 patients each. All patients received an intrauterine installation of either 5 mL of 2% lidocaine or sterile saline by way of 18-gauge catheter, and either 550 mg naproxen sodium or placebo by mouth. The catheter was left in place for 3 minutes to minimize loss of fluid. Each Pipelle sampling was performed using a minimum of 3 passes. Pain was rated by both patient and physician.

Although the pain reported by the patients in the naproxen-only and lidocaine-only groups were 18% and 17%, respectively, less than the placebo group, these figures were not statistically significant. Similarly, when both active drugs were used, they were not statistically better than either drug alone, but the combination was significantly better than placebo. The same findings were reported in the sub-group of postmenopausal patients. The physician-reported scores also showed significant benefit for the combination.

COMMENT BY FRANK W. LING, MD

This is a beautifully designed study, presenting Level I evidence at its best. Endometrial sampling using the Pipelle or similar instrument is a very common procedure in the gynecologist's everyday office practice. When patients can be made more comfortable, each of us needs to look carefully at how it could positively affect our own practice style. Admittedly, the amount of discomfort is related to your own "pre-operative" technique. I have personally observed a lot of residents in training perform such a biopsy with varying results. Often it relates as much to the interpersonal contact that is maintained with the patient as it is the manual technique that is used. This is entirely separate from the issue of using oral nonsteroidals, intrauterine installation of lidocaine, or both.

Merely telling the patient what you are doing before doing it makes a huge difference. It is the same principle as is taught when a pelvic examination is done. "Talk, then touch." If the patient knows what is going to be done before it is, she is that much better able to tolerate it because it is no longer a surprise or unexpected. Dogan and colleagues don't say how much of that "verbal anesthesia" is used in the study, but each of us should recognize that the reassurance and comfort that a patient derives from us telling her what we are doing is not inconsequential.

Dogan et al are correct in pointing out that a tenaculum on the cervix is not mandatory in all cases. I am confident that each of us tests each patient to see if we can get by without using it. If I find that it is necessary, I use the distraction technique to apply it initially, ie, I ask the patient to cough a couple of times as I close the tenaculum to the first notch. That will help bring about some reduction in the initial pain perception, then I will tell the patient that I am going to close the instrument a little more (I don't use the word "clamp"), which might cause some more discomfort (I don't use the word "pain").

Passing the Pipelle is often quite easy, but sometimes obstruction is met. I typically perform a bimanual examination beforehand to determine if the uterus is anteverted/retroverted and anteflexed/retroflexed to aid my "aiming" of the Pipelle. I do not sound the uterus, since I believe that the bimanual tells me how large the cavity is approximately, and also that the use of a uterine sound is an invitation to causing a perforation. The one exception that will cause me to use a sound is when the Pipelle will not pass initially, then it won't even pass when I grasp it with a ring forceps in an attempt to guide it into the cavity.

There are a couple of other techniques which may prove beneficial occasionally, both of particular value if a patient has a relatively stenotic cervical os. I hear people talk bout lacrimal duct probes being helpful, but I personally find the wooden end of a small cotton swab to be of equal or greater utility. Also, as a last ditch effort to avoid taking a patient to the operating room with its risks and costs: try a #11 blade to open the dimple which is the remnant of the os. Pushing it in slightly, then removing it and rotating it 90° for another incision creates an entry into the endocervical canal.

So in the routine of our daily practices, perhaps the use of lidocaine with oral naproxen sodium should be considered for our Pipelle biopsies. Certainly endometrial-sampling techniques should be scrutinized just as any other aspect of our practice. If we make our patient's experience better, then we should go for it.

Ovarian Carcinoma Treated with High-Dose Chemotherapy and Autologous Stem Cell Transplantation

ABSTRACT & COMMENTARY

Synopsis: *Patients in clinical remission are most likely to benefit from autologous transplantation, with the exception of patients with clear cell histology.*

Source: Donato ML, et al. *Bone Marrow Transplant*. 2004 May 3. (E-pub ahead of print).

In an effort to identify important characteristics defining progression-free and overall survival in patients with advanced-stage recurrent or progressive

ovarian cancer, Donato and colleagues studied 96 patients undergoing 3 high-dose chemotherapy regimens. Over the 77-month accrual period, 102 autologous peripheral stem cell transplantations were delivered. The regimens studied were paclitaxel and carboplatin (PC), topotecan-melphalan-cyclophosphamide (TMC), and cyclophosphamide-BCNU-thiotepa (CBT). A heterogeneous cohort of patients made up the study population including 43% in clinical complete response, 34% in partial response to prior chemotherapy, 18% with progressive disease, and 5% with stable disease. Repeat transplantation was administered to 6 patients. The majority of the patient cohort had serous histology although a small subset was clear cell carcinoma. All patients were required to be "physiologically" 60 years of age or younger and have adequate metabolic chemistries. Differing methodologies for blood stem cell mobilization and collection were used over the years of the trial representing refinement in technique, but importantly no transplant-related mortality was observed. Median follow-up for the entire study population was 18 months (3.5-68 months).

Overall, the 6-year survival was 38%. For patients receiving transplantation for remission consolidation, the 6-year survival was 53% and progression-free survival, 29% (median 20 months). Evaluating important predictive survival characteristics, Donato and associates identified clear cell histology and disease status other than complete remission as adverse prognostic factors. Although different populations were studied among the 3 regimens, the TMC combination appeared to be superior for survival characteristics, likely representing the benefit from chemotherapeutics that are non-cross resistant with standard front-line agents. Donato et al call for continued work in the consolidation setting given the results from this patient collection.

COMMENT BY ROBERT L. COLEMAN, MD

It is a not uncommon occurrence and a distinctly disappointing situation when a patient's tumor recurs after being declared "in remission." The chemosensitivity of ovarian cancer lends itself fittingly to the emotional roller coaster a patient suffers following the frequent regression-and-recurrence cycle that this difficult-to-eradicate tumor poses. Unfortunately, it is well documented that most patients who suffer a recurrence ultimately lose this war despite an occasional battle win. Many efforts to derail this pattern have been tried including modifications to surgery, chemotherapy, and even radiation. Novel strategies such as prolonged standard chemotherapy, high-dose chemotherapy, intraperitoneal chemotherapy and radiation, consolidation chemotherapy, biological therapy, and gene therapy have been investigated with few, if any, demonstrating clear survival advantage to these patients. Nonetheless the endeavor continues, as the prize is high.

The current study by Donato et al is a good example of the effort being extended. One treasured end point of solid tumor chemotherapy treatment is to find a way to overcome acquired resistance to conventional agents. Bolstered by in vitro and in vivo data of a dose-response correlation, high-dose chemotherapy would seemingly be a "high-benefit" approach, if it could be delivered safely. Previous work in dose intensification using conventional agents without hematopoietic support has not shown an advantage; and initial evaluation of high-dose strategies demonstrated excessive toxicity. However, much has been learned about this latter technique including use of peripheral blood to source hematopoietic progenitors, improved supportive care, and better patient selection. Morbidity and mortality from high-dose chemotherapy has dropped significantly and evaluation of specific myeloablative chemotherapy combinations, as seen in the current study, has been accomplished.

While the results from this and other single institution high-dose series show some promising response and survival characteristics, they are difficult to evaluate not only against one another but also against our collective experience with conventionally dosed chemotherapy.[1,2] Donato et al argue that those patients in clinical remission or those found with minimal disease at second look represent the best patients to undergo this intensive treatment. This same patient population has also been targeted for conventionally dosed consolidation strategies. In a recent randomized trial comparing 3 vs 12 cycles of intravenous paclitaxel in patients with clinical remission (Gynecologic Oncology Group Trial #178), Markman and colleagues reported the 12-cycle arm produced a significantly improved median progression free survival of 29 months.[3] This seemingly compares favorably with the 20-month progression-free survival reported by Donato et al in the current report. Survival data are not available in the GOG study, so it is unknown in what context the observed 53% 6-year survival would abide. However, this number is laudable and the oncology community would welcome further development of this modality if it can safely improve the lives women with ovarian cancer. ■

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Ultrasonographic Occiput Position in Early Labor in the Prediction of Cesarean Section

ABSTRACT & COMMENTARY

Synopsis: *The occiput posterior relationship with Cesarean section is worth exploring.*

Source: Akmal S, et al. *BJOG*. 2004;111:532-536.

An enlightening article recently appeared in the *British Journal of Obstetrics and Gynaecology* by Akmal and colleagues. They performed sonograms in 601 women in active labor to assess the position of the fetal head as it entered the maternal pelvis. Using the simple end point of Cesarean section, they then folded in a variety of other variables, such as maternal age, parity, maternal height, ethnicity, fetal gender, gestational age, and whether labor was spontaneous or induced.

Eighty-seven patients had Cesarean sections (14%) in the study. A major difference in Cesarean section rates (CSR) was noted between those with occiput posterior positions in early labor (19%) and those with other cephalic positions (11%). The variables most associated with Cesarean section are outlined in the Table, lifted directly from the paper.

Most of the indicators are not surprising, but some are, such as fetal sex. Akmal and colleagues then developed a scoring system based on the above variables and came up with a probability score for an individual entering labor. Interestingly, 337 patients (63%) had low scores (below a preset threshold), and their positive predictive value for Cesarean section was 4%. However, the remaining 224 (37%) who had scores above this threshold had CSR's between 32% for the lower score and 56% for the highest.

Table

Multiple Regression for the Prediction of Cesarean Section

Parameter	Odds ratio (95% CI)	*P* value
Maternal age	1.1 (1.0-1.2)	< 0.0001
Afro-Caribbean	2.4 (1.2-4.6)	0.013
Height	0.93 (0.89-0.97)	0.002
Parity	0.2 (0.1-0.4)	< 0.0001
Type of labor	2.2 (1.3-3.8)	0.004
Gestation	1.4 (1.1-1.7)	0.003
Head descent	0.6 (0.4-0.9)	0.012
Occiput posterior	2.2 (1.3-3.7)	0.004
Male gender	2.0 (1.2-3.5)	0.009

COMMENT BY JOHN C. HOBBINS, MD

At first, I thought there was nothing new in this study, and the idea of rating a patient's chances of a successful vaginal delivery (ahead of time) is not new and, in fact, has been very recently revisited.[1] However, the addition of assessment of head position through ultrasound is a new wrinkle and, using the variables published in this article, the CSR in those with low scores (making up the majority of patients) was only 4%.

Akmal et al explain the increased odds ratios for the variables in various ways and cite literature to support their reasons. For example, short mothers and those of Afro-Caribbean ancestry tend to have smaller or non-gynecoid pelves. Older women have uteri that need more oxytocic help and their providers tend to have a lower bail out threshold for them. Multiparas require less uterine effort to accomplish early cervical dilation, and induced labors have always had a higher CSR, probably because the uterus is not ready for labor, coupled with the reasons for the induction in the first place.

The factor that is not as easy to explain is the 2-fold higher CSR for male fetuses. Akmal et al reference a study showing that male fetuses have a lowered ability to release catecholamines in response to fetal hypoxia/acidosis, and therefore, are more susceptible to fetal distress.[2] This one I have trouble swallowing, especially since there is no evidence in the paper for a higher CSR for fetal compromise in male fetuses.

The occiput posterior relationship with Cesarean section is worth exploring. There is evidence that persistent occiput posteriors result more frequently from the relationship between the occiput and the pelvic inlet, rather than from an inherent inability to rotate during passage through the midpelvis. That would mean that the die is cast early, rather than late.

Now—what do we do with this information in clinical practice? First, those with low probabilities for Cesareans should be given every chance for a vaginal delivery short of fetal compromise. Also, those with a high probability for Cesarean section should have an opportunity to have a vaginal delivery, but if they fall off the labor curve at any time along the way, it might be judicious to avoid postponing the inevitable.

Akmal et al made a pitch for a Dublin-like approach of active management of labor in those patients with a high probability for Cesarean, and cite a recent randomized clinical trial (RCT) showing a benefit from this approach. However, although it may make sense to make

a short but aggressive try at vaginal delivery, some RCTs have not validated the active management of labor approach, and the study cited did not address specifically patients with high probabilities for Cesarean sections.[3-6]

Last, using ultrasound to assess the position of the fetal occiput in early labor should yield important adjunctive information in later decision making. ■

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Laparoscopic Uterine Vessel Occlusion vs Uterine Artery Embolization for Fibroids

ABSTRACT & COMMENTARY

Synopsis: *In a comparison with uterine artery embolization, laparoscopic occlusion of uterine vessels for the treatment of symptomatic uterine fibroids had less associated postoperative pain and comparable effects on fibroid-associated symptoms.*

Source: Hald K, et al. *Am J Obstet Gynecol*. 2004;190: 37-43.

THIS NORWEGIAN STUDY EVALUATED THE OUTCOMES IN 46 premenopausal women with symptomatic fibroids who underwent either uterine artery embolization (UAE) or laparoscopic closure of the uterine arteries. There were 24 patients assigned to UAE, and 22 to laparoscopy, but not randomly so. Patients were considered candidates for laparoscopy if the uterus did not reach above the umbilicus on physical examination.

The UAE technique used polyvinyl alcohol particles. The laparoscopic procedure included the following features: legs in "frogleg" position, without abducting the legs; Foley catheter during and after surgery for 24 hours; a 10 mm intraumbilical port and 2 lower quadrant ports; incisions of the peritoneum between the round and infundibulopelvic ligaments; occlusion of the uterine artery at the level of the internal iliac artery with a clip; bipolar cauterization of the collateral arteries in the utero-ovarian ligament.

Closure of the uterine vessels was accomplished in all 22 patients with 3 suspected of having obturator nerve damage. All but 1 UAE was successful, the one failure due to bilateral vessel spasm. Two patients in each group had temporary increases in FSH levels. Both groups had significant reduction in menorrhagia and also reduction in uterine volume as well as the size of the dominant fibroid. Patients undergoing UAE used significantly more analgesics than the surgical group.

COMMENT BY FRANK W. LING, MD

Here's the latest option that your patients will be asking about (if they haven't already). It used to be hysterectomy or myomectomy. Then both could be done through the laparoscope. Then myolysis came along. Then the radiologists got involved because they could offer UAE. Now the gynecologists try to recapture some of their old clinical turf by occluding vessels endoscopically. Oh yeah, and don't forget about GnRH agonist to shrink the size of the fibroids. It's FDA approved to shrink them preoperatively, but let's face it: sometimes that planned surgery doesn't occur. It all seems pretty logical to me, but to patients (and sometimes to their physicians who are trying to counsel them), the choices can be a bit daunting.

Which is best for me, doctor? Which technique is tried and true? Which is too new, too experimental? For that matter, what will the insurer pay for? Yes, that last question definitely makes a difference! When informed consent is being provided a patient with symptomatic fibroids, should this laparoscopic technique be included as a viable option? I would venture to say that as yet, the data need to be more compelling for me to suggest this procedure to a patient. For that matter, I'm not convinced that UAE is all that it's cracked up to be. I don't mean to sound cynical, but I've not seen radiologists achieve enough success, at least in the medical community in which I practice, for UAE to be touted as the "gold standard" for fibroid treatment.

It may sound too simplistic, but we know that a hysterectomy will address the symptoms of large fibroids, whether it's pressure sensation, pain, bleeding, etc. Yes, it carries with it significant potential morbidity, but that morbidity is well known, both to the surgeon as well as the patient. Similarly, myomectomy has enough of a track record so that a patient can be well informed what might lie ahead. Particularly in cases of multiple fibroids, none of us can predict what the outcome of the myomectomy will be, especially if preservation of the uterus is the top priority and hysterectomy is to be

avoided at all costs. If your experience with UAE is at all similar to that of many of your colleagues, you have seen some patients have excellent results, while others have been less than satisfactory.

In any medical community, some physicians embrace new techniques sooner than others. Similarly, some are just better than others at any given procedure. Just as not all gynecologic surgeons are created equal, not all interventional radiologists are created equal. It makes sense to speak with those with whom you share patients with symptomatic fibroids to make sure that patients are given data that truly applies to them, ie, a patient should get informed consent about UAE or laparoscopic vessel occlusion based on experience that her physicians have had, not idealized from the literature in which experts with far greater expertise are quoted.

One of the greatest services that we can provide our patients is to put what they read and hear in perspective. That includes what they are exposed to on the Internet, on television, in the lay press, as well as from other physicians. As of now, the laparoscopic occlusion of uterine vessels is an intriguing option that holds some promise, but is certainly not a panacea. For that matter, I would place UAE in that same category.

So, in summary, this article, a self-described pilot study, compared 2 options for the treatment of symptomatic fibroids, both of which still need lots of study before they become more "mainstream" for the general population. ■

Genomic Imprinting in Disruptive Spermatogensis

ABSTRACT & COMMENTARY

Synopsis: *Oligoasthenospermia (male factor infertility) is associated with abnormal genomic imprinting of the sperm, a feature that may predispose to abnormal embryogenesis, including a risk of rare developmental abnormalities and cancer in adulthood, if fertilization occurs, as it may because of the availability of assisted reproductive techniques.*

Source: Marques CJ, et al. *Lancet*. 2004;363: 1700-1702.

It is commonplace to suspect that technological breakthroughs are not without risks. Although assisted reproductive technologies have aided many couples in their quest to become parents, there has always been a concern about the potential risks. The present article reveals one of the mechanisms that may result in abnormal, but nonlethal, embryogenesis. Genomic imprinting is a nonrandom event by which either the paternal or maternal allele is "silenced" after fertilization. Silencing is necessary to control gene dosage. Genomic silencing is not random and the gene to be silenced depends on the sex of embryo. Sometimes the maternal allele is silenced and sometimes the paternal allele. Assisted reproductive technologies have been associated with a rise in syndromes that are thought to represent abnormal genomic imprinting, including Angelman's syndrome and Beckwith-Wiedeman's syndrome. It has been suggested that the methods by which embryos are cultured in the laboratory are responsible for abnormal gene silencing. In the present study, Marques and colleagues tested the hypothesis that, at least in some instances, abnormal male gametes may confer abnormal genomic imprinting.

To test the hypothesis that abnormal sperm may harbor abnormal genomic imprinting, Marques et al looked at methylation pattens of the DNA of sperm of men undergoing assisted reproduction. Methylation of cytosine in CpG islands is the main mechanism by which genes are silenced. The methylation patterns are erased in embryonic germ cells and then reset during gametogenesis or after fertilization. Marques et al examined methylation patterns in spermatozoan DNA from semen samples from 123 normozoospermic and oligozoospermic men undergoing routine semen analysis for infertility diagnosis. The maternal imprint was correctly erased in all normozoospermic and oliogzoospermic samples. Paternal imprinting was normal in all men with a normal semen analysis (> 20 million sperm/mL with normal motion and morphology), but abnormal in 24% of men with oligozoospermia. In men with mild oligospermia, the rate of abnormal paternal methylation was 17%, and in men with severe oligospermia, it was 30%.

■ COMMENT BY SARAH L. BERGA, MD

There is no sense shutting one's eyes to the downsides of technology. One intuitively senses that tampering with mother nature cuts both ways. To tamper, I believe, is an inherent human legacy and we have been at it forever. It is arguably better, I fear, to understand the trade-offs so that one can counsel appropriately than it is to glibly assume that there are no risks. The benefit of knowing, however, is not to proscribe, but rather to enlighten those who must choose. Life and life-assisting technologies have both known and hidden risks. Failure to conceive is devastating and has profound psychological implications. Thus, it is no wonder that couples seek remedies. To the extent that we can, we must describe the pros and cons. If the individuals

faced with such decisions understood some of the risks, would they choose differently? It is difficult to know what one would do unless one was faced with the decision.

The results of the present study suggest that abnormal sperm may give rise to abnormal offspring because of abnormal genomic imprinting in the sperm. While this may seem surprising, it is important to recognize that this is an inherent risk and not one that is likely to go away merely by improving embryo culture methodologies. Perhaps it will be something that we can learn to screen for, either in the sperm or in the embryos.

The present study is not definitive. The study does not prove that the abnormal methylation patterns in sperm were capable of being transmitted to embryos. Perhaps embryos with abnormal paternal imprinting do not do well in the laboratory and are unlikely to be transferred. Perhaps embryos that result from sperm with abnormal genomic imprinting do not implant with great success. It is important to remember that even technological advances carry built-in safeguards. ■

CME Questions

1. **Genomic imprinting refers to:**
   a. the process by which the diet of the mother predisposes the fetus to diabetes in later life.
   b. the process whereby the fetus recognizes certain features of the gestational mother, such as voice, smell, and heart rate.
   c. the process whereby one gene, either paternal or maternal in origin, is silenced so as to provide correct gene dosage.
   d. the process whereby genes in the oocyte are regulated.
   e. a random event that silences either the paternal or maternal allele at the time of fertilization.

2. **Which of the following techniques is best in reducing pain associated with Pipelle biopsies?**
   a. oral naproxen sodium
   b. intrauterine installation of 2% lidocaine
   c. paracervical block
   d. pudendal block
   e. a and b

3. **The following are effective treatments for symptomatic fibroids *except*:**
   a. myomectomy
   b. uterine artery embolization
   c. depot provera
   d. laparoscopic occlusion of uterine vessels
   e. GnRH agonist

Answers: 1 (c); 2 (e); 3 (c)

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Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Britain to Allow Over-the-Counter Sales of Zocor

The British government will soon allow over-the-counter (OTC) sales of Merck's simvastatin (Zocor), marking the first time any country has allowed the OTC sale of a statin. The drug lost its patent protection in England last year, and Merck is eager to make up for some lost revenues by entering the lucrative OTC market. It is likely the drug will be available in an OTC dose of 10 mg. Pharmacists will be asked to carry out a simple screening questionnaire on the spot to screen for appropriateness and safety. Not everyone is happy about the OTC switch however. An editorial in the British journal *Lancet* stated that there is insufficient evidence to justify the OTC switch and implied that the British government is simply trying to save money by defraying prescription drugs costs. Currently over 1.8 million patients in England take statins at a cost of over $1.1 billion per year.

FDA Rejects Plan B Bid

FDA regulators have rejected a bid from Barr Pharmaceuticals to market their "morning after pill" as an OTC. The product, called Plan B, contains 0.75 mg of levonorgestrel, a progestin commonly used in birth control pills. Plan B is marketed as an emergency contraceptive that can be used up to 72 hours after unprotected intercourse or suspected contraceptive failure. The decision by the FDA was somewhat surprising as it went against the recommendation the agency's own advisers who, last December, voted overwhelmingly in favor of the over-the-counter switch for Plan B. The decision prompted some groups to suggest that political pressure from the Bush administration was responsible for the denial. The FDA, however, stated in its rejection letter that they were concerned about the safety of the product for younger women, and kept the door open by suggesting that more data may prompt a reconsideration. In the meantime, Plan B is still available by prescription.

Recombinant Erythropoietin Products May Stimulate Tumor Growth

Two recent studies have raised the question of whether recombinant erythropoietin products may stimulate tumor growth in cancer patients. One study, published in the October 2003 *Lancet*, reviewed 351 adult patients with head neck cancer who were randomized to subcutaneous erythropoietin or placebo 3 times weekly prior to radiation therapy and continuing throughout radiation therapy. Patients treated with erythropoietin had improved hemoglobin concentrations, but otherwise had poor outcomes. Median locoregional progression-free survival was 745 days with placebo and 406 days with erythropoietin (relative risk, 1.62; [95% CI, 1.22-2.14]; P = .0008). Overall,

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over the 4 years of study, 52% of placebo-treated patients died, compared to 61% of erythropoietin treated patients (RR 1.39; [95% CI, 1.05-1.82]; P = .02). A second study in Europe of erythropoietin in breast cancer patients was terminated early because patients receiving the drug had lower 12 month survival rates than patients receiving placebo (70% vs 76%; P = .0117). An editorial in the December 17th Journal of the National Cancer Institute reviewed this issue and raised the plausibility of the findings. The authors noted that erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. They also noted that the preliminary data suggest that some of these cancers may proliferate in the presence of erythropoietin.

The editorial concluded by calling for more research into the possible relationship between erythropoietin and poor outcomes in the treatment of cancer patients. The FDA's Oncologic Drugs Advisory Committee recently met in May, and backed a proposal by Johnson & Johnson (makers of Procrit) and Amgen (makers of Aranesp) to study this issue. The exact design of these studies is still to be delineated, but both companies have pledged to collaborate on such research.

Rosuvastatin: Market's Most Potent Statin

Rosuvastatin (Crestor-Astra Zeneca) appears to be the most potent statin currently marketed. In a study of 3140 patients with CAD, atherosclerosis, or type 2 diabetes, patients were randomized to rosuvastatin 10 mg, atorvastatin 10 or 20 mg, simvastatin 20 mg, or pravastatin 40 mg for 8 weeks. Patients either remained on these treatments or were switched from other statins to rosuvastatin. The primary pinpoint was a LDL cholesterol of < 116 mg/dL. Significant improvement in LDL cholesterol goal achievement was found for patients who were switched to rosuvastatin 10 mg compared with patients who remained on atorvastatin 10 mg (86% vs 80%; P < 0.5), simvastatin 20 mg (86% vs 72%, P <.001), and pravastatin 40 mg (88% vs 66%, P < .0001). For patients who were switched from atorvastatin 20 mg to rosuvastatin 20 mg, the rate at goal was 90% vs 84% (P < .01) (*Am Heart J*. 2004;147:705-712). But while rosuvastatin appears to be the most potent statin, it may carry a higher dose related risk of muscle toxicity including myositis and rhabdomyolysis. Astra Zeneca has recently acknowledged 4 cases of rhabdomyolysis in patients who were taking 40 mg of rosuvastatin, and has urged physicians in England to avoid initial high dose therapy with the drug, instead starting at 10 mg and titrating with appropriate follow-up.

FDA Actions

Immunex Corp.'s etanercept (Enbrel) has been approved for use in patients older than the age of 18 with moderate-to-severe plaque psoriasis. Enbrel is currently marketed for use in patients with ankylosing spondylitis, psoriatic arthritis, moderate to severe rheumatoid arthritis, and juvenile rheumatoid arthritis. The expansion of indications to treat psoriasis was expected after 2 phases.

All studies showed improvement with treatment up to 1 year. Etanercept, which is a tumor necrosis factor inhibitor, joins the biologics alefcept (Amevive) and efalizumab (Raptiva) in the suddenly rather crowded market for the treatment of psoriasis.

The FDA has approved Indevus Pharmaceutical's trospium chloride (Sanctura), for the treatment of overactive bladder with symptoms of the urge urinary incontinence, urgency and frequency. The drug is a muscarinic receptor antagonist, and as such, has side effects that include dry mouth and constipation. It is, however, relatively well-tolerated with fewer drug-drug interactions than currently available medications.

Fondaparinux (Arixtra-Fonda BV), the synthetic selective factor Xa inhibitor, has been given the expanded indication for treatment of acute pulmonary embolism and acute deep venous thrombosis without PE when coadministered with warfarin. Previously, the drug had been approved for prevention of DVT in the setting of orthopedic surgery.

Salix Pharmaceuticals has received approval to market rifaximin (Xifaxan) for the treatment of travelers diarrhea caused by noninvasive strains of *Escherichia coli*. The drug is unique in that it is minimally absorbed (< 0.5%) after oral administration, and exerts its action only in the gut. It is not for use in patients with diarrhea associated with fever or bloody stools, or pathogens other than *E. coli*. The drug is approved for patients age 12 and older and appears to be well-tolerated. ■