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INSIDE

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Congenital Malformations and ART: Risks and Implications for Prenatal Diagnosis and Fetal Medicine

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics,
University of Colorado Health Sciences Center, Denver

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Incidence of some types of congenital anomalies after ART is increased to the point where heightened surveillance is indicated.*

Source: Williams C, et al. Congenital malformations after assisted reproduction: Risks and implications for prenatal diagnosis and fetal medicine. *Ultrasound Obstet Gynecol* 2010;35:255-259.

Louise Brown, the first baby conceived through in-vitro fertilization (IVF), was born in England in 1978. Since then, there has been a steady rise in births conceived through various forms of assisted reproductive technology (ART), to a point where about 25% of live births now in the United Kingdom have been conceived through ART. In the United States, 1% of babies born in 2006 were through ART.

Unfortunately, pregnancies conceived through ART have been shown to be associated with higher rates of various complications, and very recently a group of British investigators summarized the data available on one facet — congenital anomalies.

In this review, two meta-analyses were cited, showing a 30% higher rate of major congenital anomalies in children born after ART than those conceived spontaneously. This is in sync with a very recent Swedish registry study,[1] involving 16,000 ART children, which showed a 42% increase in congenital anomalies. The largest increase has been in cardiovascular anomalies (a 4-fold risk).[2] Specifically, septal defects were the most common anomalies seen after ART (odds ratio, 2.6; 95% confidence interval, 2.2-3.1),[1] but the greatest rise in

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ART-conceived pregnancies, first noted 20 years ago and reiterated by Williams et al, occurred with transposition of the great vessels (a 4-fold increase).

Other fetal abnormalities included neural tube defects (5-fold increase),[1] oral facial defects (2.5-fold increase),[1] and syndromes representative of defects in genetic imprinting such as Beckwith-Wiedemann syndrome.[3] Interestingly, hypospadias in male infants was predominantly increased in those conceived through intracytoplasmic sperm injection (ICSI).[4] The authors of the editorial point out that most of the studies in the review corrected for maternal age, parity, and multiple gestation (all of which can increase the risk of anomalies).

The nagging question of why this is happening is difficult to answer. Yes, women who are having difficulty getting pregnant are more prone to have offspring with anomalies, but adding ART to the mix seems to further accelerate this tendency.[5] Multiple pregnancies are more often associated with anomalies, but when comparing apples to apples (ART multiples with spontaneously conceived multiples, and ART singletons with non-ART singletons), there still are significant differences. So the problem seems to be related more to the process, rather than the host.

COMMENTARY

Many thousands of previously infertile couples have been helped by various forms of ART. However, this wonderful technology has come with a price (literally and figuratively). It is now clear that the women or insurance companies willing to shell out about $12,000 per try at IVF will also have to deal with the fallout, which involves a 48% chance of twins (2006 CDC statistics)[6] — along with the accompanying increased rates of prematurity, low birth weight, fetal growth restriction, and cerebral palsy. Even in singletons, the rates of these complications after ART are higher than in spontaneously conceived singletons. Now it is clear that congenital anomalies are also part of this fallout.

The way to prevent complications from multiple gestations is to prevent multiple gestations from happening, and it is heartening that between 2004 and 2006 the rate of twins leveled off (32/1000 to 32.1/1000 live births).[6] However, a 48% rate of twins with ART is too high. Regarding fetal anomalies, since it is unclear what is responsible for their greater presence after ART, it will be difficult to prevent them. However, at least we should be able to identify them early in pregnancy or, better yet, to assure these already wired patients that their babies do not have any of the above anomalies. Since today's prenatal diagnostic motto is "the earlier the better," a very thorough first trimester scan should allow the provider to identify fetal number (and if twins, to determine chorionicity). Since there is a relationship between the size of the nuchal translucency (NT) and cardiac anomalies, an NT assessment at 11-14 weeks can be extremely helpful. A recent study shows that by adding a Doppler evaluation of the ductus venosus at that time, 50% of cardiac anomalies can be screened in.[7] Today the ultimate diagnosis can often be made with a full fetal echocardiogram by transvaginal ultrasound by 15 weeks. Obviously, should this exam be incomplete, it can be accomplished later with excellent sensitivity. Open neural tube defects should be identified with virtually 100% accuracy by ultrasound by 16-18 weeks and Beckwith-Wiedemann syndrome can be suspected when an omphalocoele is seen after 12 weeks. Hypospadias can be detected effectively with 3-D ultrasound in the second trimester.

So, ART patients with singletons or multiple gestations can benefit from:

- An early first trimester scan to assess the viability and number.
- An NT evaluation with a Doppler assessment of the ductus, if possible.
- An early attempt at 12-15 weeks at a transvaginal fetal echocardiogram, if either the NT or ductus is abnormal.
- A detailed ultrasound survey of the fetal anatomy, with markers for Down syndrome if the patient is > age 34 with a singleton or 32 years old with di/di twins.
- A full fetal echocardiogram at 20-24 weeks for all.

Note: Since the incidence of vasa previa is about 1 in 290 pregnancies conceived through IVF,[8] an attempt should be made to identify the location of the placental

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Questions & Comments
Call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

cord insertion in one of the above exams.

If the results from these examinations are unremarkable, then these patients can be reassured that the likelihood of their fetuses having an anomaly is extremely small.

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Fertility-sparing Surgery in Ovarian Cancer: Is It Safe?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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M.D. Anderson Cancer Center, Houston

Dr. Coleman is a consultant to GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer, and serves on the speakers bureau for GlaxoSmithKline, Eli Lilly Co., and OrthoBiotech.

Synopsis: *Patients with early-stage ovarian cancer can in many circumstances be treated with conservative surgery enabling subsequent fertility options. However, options are more limited for those with grade 3 tumors and prudence should be exercised when adjuvant chemotherapy is indicated.*

Source: Satoh T, et al. Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: A proposal for patient selection. *J Clin Oncol* 2010;28:1727-1732.

Early-stage ovarian cancer is frequently associated with younger patients, some of whom may be interested in fertility preservation. The objective of this retrospective, multicenter survey was to assess the clinical outcomes and fertility in patients treated conservatively for unilateral stage I invasive epithelial ovarian cancer. In all, 211 patients underwent unilateral oophorectomy or cystectomy for apparent localized disease. Histology, grade, description of capsular rupture at exploration, adjuvant surgical procedures, such as omentectomy and lymph node evaluation, cytology, and use of adjuvant chemotherapy were recorded. The authors classified "favorable" histology as grade 1 or grade 2 adenocarcinoma, excluding clear cell histology. Stage IC was subclassified on the basis of capsular rupture vs tumor on the external surface vs positive cytology. Most of the patients had stage IA disease (60%); the remainder was stage IC. Staging operations were not performed in 52% of patients and when done, were complete in just 13%. Nevertheless, 5-year overall and recurrence-free survival were 100% and 98% for stage IA/favorable histology, 100% and 100% for Stage IA/clear cell histology, 100% and 33% for stage IA/grade 3, 97% and 92% for stage IC/favorable histology, 93% and 66% for Stage IC/clear cell histology, and 67% and 67% for stage IC/grade 3. Forty-five (53.6%) of 84 patients who attempted conception gave birth to 56 healthy children. The authors conclude that fertility-sparing surgery is a safe treatment for stage IA patients with favorable histology and suggest that stage IA patients with clear cell histology and stage IC patients with favorable histology can be candidates for fertility-sparing surgery followed by adjuvant chemotherapy.

COMMENTARY

In light of its clinical reputation, ovarian cancer is seldom considered a disease where fertility-sparing options abound. In fact, we have made it a battle cry to formally stage patients with apparent limited invasive disease because metastatic disease is found in nearly a third and failure to recognize this can have lethal consequences. This being said, patients with limited disease are typically younger, have more favorable histology, and many will be cured with local extirpation alone. Fertility preservation may be an acceptable option for these women. Unfortunately, evidence to support this recommendation remains elusive, and what's available is contradictory at times, marred by retrospective interpretation, collected over prolonged enrollment periods, and limited by inconsistent surgical and adjuvant chemotherapy management patterns. Nevertheless, the current report has amassed enough data

Table. Authors' recommendation regarding fertility-sparing surgery in appropriate patients with unilateral stage I ovarian cancer.

	Histology/Grade		
Stage	Favorable (mucinous, serous, endometrioid, grade 1 or 2)	Clear cell	Grade 3
IA	Reasonable	Optional but with chemotherapy	Risky
	(n = 108; 100%/98%)	(n = 15; 100%/100%)	(n = 3; 100%/33%)
IC	Optional but with chemotherapy	Risky	Risky
	(n = 67; 97%/92%)	(n = 15; 93%/66%)	(n = 3; 67%/67%)

Note: Summary of the number of patients and 5-year overall and relapse-free survival are in parentheses

to raise the hypothesis that certain cohorts of these patients may be safely managed conservatively with favorable survival and normal fecundity. The data are summarized in the Table *(above)*. However, it is important to recognize that even in this relatively large study, the number of patients in each category is unbalanced and may be too small to make an interpretation, and there are considerations that may confound their recommendations. For instance, 60% of the patients were of mucinous histology. Since most mucinous tumors present with limited stage disease, this histology over-represents the favorable category and limits interpretation of safety in the other histologies. Second, few patients underwent formal staging procedures. The authors' recommendations were influenced by what they termed "lethal recurrence," wherein subcategories of patients had unfavorable outcomes despite fertility-sparing procedures. An alternative conclusion may have been reached had staging pathology been available in these cases. It's of importance to note that while all patients with isolated recurrence in the residual ovary (n = 5) were salvaged with subsequent therapy, only 3 of 13 patients (23%) were salvaged when recurrence appeared outside of the residual ovary. Further, observed amenorrhea and secondary infertility accompanied the administration of chemotherapy, supporting their recommendation to exercise caution in patients with favorable histology and apparent stage IA disease; however, use of chemotherapy as adjuvant therapy is common in patients without proper staging information. This makes it more difficult in adjudicating the proper management strategy in a woman with apparent, but formally unstaged, limited disease who wishes to maximize survival and preserve fertility. Because it is essentially impossible to study fertility-sparing surgery by randomized trial, these data provide some confidence that this option is feasible for some patients.

Additional Reading

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Dietary Fat Consumption and Risk of Endometriosis

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Consumption of* trans *fats increases the risk of endometriosis, while long-chain omega-3 fats are protective.*

Source: Missmer SA, et al. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod* 2010 March 23; Epub ahead of print.

To investigate the relation between dietary fat intake and the risk of endometriosis, these authors analyzed 12 years of prospective data from the Nurses' Health Study II that began in 1989. Dietary fat was assessed via validated food-frequency questionnaire in 1991, 1995, and 1999 and averaged over the three diet questionnaires. The risk of a new diagnosis of laparoscopically confirmed endometriosis was assessed using a Cox proportional hazards models after adjustment for total energy intake,

parity, race, and body mass index at age 18. The cohort included 586,153 woman-years of follow-up and 1199 cases of laparoscopically confirmed endometriosis. While there was no association with total fat consumption and endometriosis risk, those women in the highest fifth of long-chain omega-3 fatty acid consumption were 22% less likely (risk rate [RR], 0.78; 95% confidence interval [CI], 0.62-0.99) to be diagnosed with endometriosis compared with those consuming at the lowest fifth. In contrast, those consuming at the highest quintile of *trans* unsaturated fat intake were 48% more likely (RR, 1.48; 95% CI, 1.17-1.88) to be diagnosed with endometriosis compared with those consuming at the lowest fifth. The tests for trends were positive for increasing consumption in both groups. These data support findings from other animal and observational studies that *trans* fat is associated with an increased risk or progression of confirmed endometriosis.

COMMENTARY

This large prospective study of diet and endometriosis demonstrates once again the impact of diet on overall health. If there were not enough reasons to avoid *trans* fats already (associated with increased risks of obesity, cardiovascular disease, stroke, Parkinson's), we can now add endometriosis. Endometriosis is a highly prevalent condition that is the third leading cause of gynecologic hospitalization. Endometriosis is also associated with pelvic pain and infertility, two important health concerns of women. Therefore, identification of a modifiable risk factor that could reduce the risk of operative intervention for endometriosis represents an important contribution that warrants careful scrutiny.

The Nurses' Health Study (NHS) was established in 1976 with funding from the National Institutes of Health to investigate the potential long-term consequences of the use of oral contraceptives, but has yielded important health information in many other areas. The selection of nurses for this long-term prospective cohort study was a deliberate design feature; their nursing education would motivate them to participate in a long-term study and yield high-quality responses to technically worded questionnaires. The initial cohort consisted of approximately 122,000 married registered nurses ages 30-55. This group has received follow-up questionnaires every 2 years with an impressive 90% response rate. To address the interaction of diet and disease, food-frequency and diet questions were added in 1980. Question related to quality of life were added in 1992. The Nurses' Health Study II cohort was established in 1989 to study these same associations in a younger (ages 25-42) population. A total of 116,686 women were enrolled in NHS II, and response rates have been the same (90%) as the original cohort. The data from the current report come from this younger population of nurses that would be expected to develop gynecologic problems. While a cohort study always suffers from potential bias, the large number of participants, excellent follow-up, multivariant adjustment of confounders, and careful independent validation of self-reported outcomes renders data of extremely high quality. Furthermore, only those women with laparoscopically diagnosed endometriosis were included as cases. Since asymptomatic endometriosis may have been discovered incidentally in women with infertility undergoing laparoscopy, this group was considered separately.

The consumption of *trans* fats correlates with high plasma lipid levels, inflammation, and arterial calcification, known risk factors for coronary heart disease (CHD).[1] They also inhibit cyclooxygenase, an enzyme required for the conversion of arachidonic acid to prostacyclin, necessary for the regulation of blood flow. Epidemiological data suggest that when *trans* fat percentages go up, death rates rise, and when *trans* fats go down, death rates go down.[1] (Just as governments justify increasing taxes on cigarettes and alcohol to recover health care costs, perhaps we should consider taxes on *trans* fat-containing food to finance our new expansion of health insurance.)

Although the FDA ruled that the amount of *trans* fat in a food item must be stated on the label after Jan. 1, 2006, the exact wording contains loopholes that permit many *trans* fat-containing foods to be sold without this warning. In contrast, omega-3 fatty acids (derived from fish oil) reduce inflammation and cardiovascular risk. Dietary supplementation with omega-3 fatty acids should be considered in the secondary prevention of cardiovascular events.[2] Even more importantly, substitution of omega-3 and polyunsaturated fats tends to reduce the overall consumption of *trans* fat.

It is important to point out that there was no association with overall fat consumption and endometriosis. This reduced the confounding influence of proportion of fat calories. What emerged was a consistent story: As *trans* fat consumption increased, so did the risk of endometriosis, and as omega-3 fat consumption increased, the risk diminished. In other words, as women shifted their diet away from pro-inflammatory *trans* fats to anti-inflammatory omega-3 fats, their risk of endometriosis decreased.

Clinicians have previously had little information to offer guidance to women who present with a significant family history of endometriosis. Compared with other modifiable risks, diet is an attractive lifestyle intervention to stress during general counseling. "You are what you eat" is more than a cliché. More than 20% of women in the cohort that reported consuming total dietary fat at the highest quintile were overweight and 18% obese, compared to only 14.8% overweight and 7.2% obese in the group reporting the lowest total fat consumption.

So we can feel even more comfortable encouraging a healthy diet in our general counseling of young women

(that Big Mac might lead to a laparoscopy for endometriosis). With the HPV vaccine and new schedules for less frequent pap tests, we need to rethink the annual exam. Get back to the basics and focus on preventive measures: A healthy diet low in *trans* fat and high in omega-3 fat, avoiding smoking, regular exercise, safe sexual practices, and effective contraception are all low-cost interventions with great benefits to patients.

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Transobturator Tape or Tension-Free Vaginal Tape for Stress Incontinence?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

Dr. Ling reports no financial relationship to this field of study.

Synopsis: *At 12 months after surgery for stress incontinence, patients who had undergone transobturator tape procedures were doing equally well when compared with patients who had tension-free vaginal tape procedures.*

Source: Ross S et al. Transobturator tape compared with tension-free vaginal tape for stress incontinence: A randomized controlled trial. *Obstet Gynecol* 2009;114:1287-1294.

One hundred ninety-nine women were randomized to undergo surgery using either the transobturator tape procedure (TOT) or the tension-free vaginal tape procedure (TVT). At 12 months, 81% and 77% of the patients in the respective groups were cured (relative risk, 1.05; 95% confidence interval, 0.90-1.23; $P = 0.577$). The tape was palpable more frequently (80% vs 27%) and more patients experienced groin pain during vaginal palpation (15% vs 6%) in the TOT patients. Quality of life improved in both groups. At 12 months, the two groups were doing equally well. Longer follow-up would be needed to identify the outcome of the palpable tapes (i.e., would they resolve or be extruded?).

COMMENTARY

I like this kind of study. It's straightforward and clear. The study design allows the author to draw conclusions. It was performed in Canadian academic and community settings with surgeons who were trained in a standardized fashion. No concurrent surgery such as hysterectomy or prolapse surgery was performed, thus allowing outcomes to be tied directly to either TOT or TVT technology. They chose to use products of a single company, in this case Boston Scientific. This eliminated any potential commercial bias.

With the endpoint at 12 months postoperative, the authors used a reasonable amount of time to assess outcome. To their credit, further follow-up is planned, pending funding. The most common TVT complication was bladder perforation, a finding compatible with that in the literature at large. Despite concern in the literature that TOT is associated with more mesh extrusion, only 1 patient in each group required re-operation for removal of an eroded mesh. Whether the increased incidence of palpable mesh after TOT leads to more extrusions remains a question to be answered with longer follow-up.

So what's the "take home" message? First, the two techniques appear to be comparable for up to 12 months. Second, having adequate training reduces the risk of complications, although it doesn't eliminate it. Third, head-to-head long-term follow-up may allow for additional conclusions to be drawn.

Nodal Resection in Ovarian Cancer: Does It Matter?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *Complete lymphadenectomy appears to be important only in those patients without post-operative residual disease following surgical cytoreduction.*

Source: Du Bois A, et al. Potential role of lymphadenectomy in advanced ovarian cancer: A combined exploratory analysis of three prospectively randomized phase III multicenter trials. *J Clin Oncol* 2010;28:1733-1739.

The prognostic value of complete cytoreduction has been well described and supported by several meta-analyses. However, the impact of lymphadenectomy is

more controversial. A previously reported randomized trial of lymphadenectomy in patients with advanced stage ovarian cancer demonstrated a benefit for the procedure only for progression-free survival (PFS), but not overall survival (OS), an endpoint it was underpowered to assess. Du Bois and colleagues combined the surgical data from three prospective phase III treatment trials performed by the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) to address the impact of lymphadenectomy OS. The data were combined because eligibility criteria between the trials were nearly the same and the trials demonstrated no treatment effect between their randomized arms. They also analyzed only data from those in whom residual disease was less than 1 cm (so called "optimal" population), and divided this cohort into those with and without any residual disease. Previous reports from this group have documented a statistically different outcome in both PFS and OS between those with (1-10 mm) and those without (no macroscopic) residual disease. They looked at three categories of node evaluation: none, limited, and complete resection. Further, they addressed a subpopulation where complete information on pre-operative and intra-operative node status was documented. Overall, data were analyzed from 1924 patients (cohort 1), of whom 1496 patients had complete pre- and intra-operative data documented regarding nodal evaluation (cohort 2). Remarkably, in both cohorts, lymphadenectomy was significantly associated with improved OS in patients without post-operative residual disease (19 and 25 months, respectively). In the larger cohort, even a limited lymphadenectomy provided a benefit in this population. However, for patients left with tumor residuum after debulking, the performance of a lymphadenectomy barely impacted OS, unless the nodes were clinically abnormal. The authors conclude that performance of lymphadenectomy appears to benefit only patients without post-operative residual disease and can only support its use in this setting. However, this hypothesis can only formally be addressed in a prospective randomized trial, which has been developed and is currently enrolling patients.

COMMENTARY

There are several concepts surrounding the subject of this study which are important to recall with respect to ovarian cancer: 1) about 20% of patients with suspected early-stage or limited disease are upstaged by formal lymphadenectomy; 2) these (stage IIIC) patients fare better than those in whom nodal status is unknown and better than other stage IIIC patients with intraperitoneal tumor; 3) patients with metastatic disease at presentation have metastatic nodal disease in about 60% of cases; 4) intra-operative assessment of nodal disease in these patients is distinctly inaccurate with about 30% of normal appearing nodes harboring metastatic disease; 5) the new standard for "optimal" cytoreduction is no visible residuum. The current study tries to bring clarity to the impact of lymphadenectomy as an isolated procedure considering these "truisms" and largely confirms the bias of most gynecologic oncologists — that the greatest impact of the procedure is in those in whom, whether by biology or surgical effort, are left with the least disease following debulking. Although the issue was seemingly resolved by a previous randomized phase III trial comparing complete pelvic and paraortic lymphadenectomy to removal of suspicious nodes alone, there are several issues to consider. These include the under-representation of truly optimally resected patients and low statistical power to address overall survival, which limited its interpretation to contemporary patient cohorts. The current report provides the necessary rationale to re-frame the question in patients most likely to benefit. Fortunately, the AGO has launched a randomized phase III clinical trial (the Lymphadenectomy in Ovarian Neoplasm [LION] Trial) to formally address this hypothesis.

Additional Readings

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2. Panici PB, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: A randomized clinical trial. *J Natl Cancer Inst* 2005;97:560-566.
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Brief Report

Half of Urban Teenaged Girls Acquire STDs within 2 Years of First Sexual Activity

HALF OF URBAN TEENAGE GIRLS MAY ACQUIRE AT LEAST one of three common sexually transmitted diseases (STDs) — chlamydia, gonorrhea, or trichomoniasis — within 2 years of becoming sexually active, according to results of a recent study.[1]

Researchers at the Indiana University School of Medicine and Regenstrief Institute, both in Indianapolis, followed 381 females enrolled at ages 14-17 in three inner-city adolescent medicine clinics. At enrollment, teens

completed a questionnaire and an interview to establish lifetime and recent sexual behaviors, as well as lifetime STD history, and were tested via cervical and vaginal specimens. Study participants returned for follow-up every 3 months for interviews and testing. In alternating quarters, they were instructed to complete daily behavioral diaries and submit weekly self-administered vaginal swabs for STD testing.

By age 15, 25% of the women acquired their first STD, with chlamydia the most common first infection. Depending on the organism, within 4-6 months after treatment of the previous infection, 25% of the women were reinfected with the same organism.

Within 2 years, about 75% of participants with an initial STD were diagnosed with a second infection, although not necessarily of the same type. Within 4 years of an initial infection, 92% of the participants had a subsequent STD.

As a result of their findings, the Indiana researchers call for STI screening in sexually active teenage girls within a year after first intercourse and for retesting of infected females every 3-4 months. Continuing surveillance might be necessary due to the continuing high risk of infection, even if the first rescreening test result is negative.[1]

Reference

1. Tu W, et al. Time from first intercourse to first sexually transmitted infection diagnosis among adolescent women. *Arch Pediatr Adolesc Med* 2009;163:1106-1111.

CME Questions

1. **Which of the following statements is *not* consistent with information from the ART review?**
   a. The rate of anomalies with ART is 30%-42% higher than in spontaneously conceived pregnancies.
   b. There is a 4-fold greater risk of fetal cardiac anomalies with ART.
   c. Septal defects are the most common cardiac anomalies seen in ART pregnancies.
   d. Open neural tube defects are not increased after ART.

2. **Which of the following is the *correct* statement?**
   a. Since 2004, the number of twin births has continued to rise in the United States.
   b. Twins have higher rates of anomalies, in general, than singletons.
   c. ART twins have similar anomaly rates to spontaneously conceived twins.
   d. Twins do not have a higher rate of cerebral palsy than singletons.

3. **What was the principle concern of the authors in making fertility-sparing recommendations for patients with stage I unilateral ovarian cancer?**
   a. Potential for lost to follow-up
   b. Potential for under-recognized metastatic disease in stage IA, G2 cancers
   c. Potential for recurrence in patients with grade 3 tumors regardless of stage
   d. The authors expressed no concerns

4. **Why did the authors feel justified in combining the data from 3 different phase III nodal resection trials?**
   a. The trials each demonstrated a benefit from experimental therapy.
   b. The eligibility for participation in each of the trials was similar.
   c. The sample sizes were large.
   d. The information regarding surgery was known.

Answers: 1. d, 2. b, 3. c, 4. b.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

In Future Issues:

Teens and Intrauterine Devices

PHARMACOLOGY WATCH

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

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.