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GYNECOLOGY

Supplemental Perioperative Oxygen and the Risk of Surgical Wound Infection: A Randomized Controlled Trial

F. Javier Belda, Luciano Aguilera, José García de la Asunción, Javier Alberti, Rosario Vicente, Lucía Ferrándiz, Rafael Rodriquez, Roque Company, Daniel I. Sessler, Gerardo Aguilar, Stephanie García Botello, and Rafael Ortí for the Spanish Reduccion de la Tasa de Infeccion Quirurgica Group

Department of Anesthesiology and Critical Care, Hospital Clínico Universitario de Valencia, Valencia, Spain

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ABSTRACT

Three hundred patients were enrolled in a double-blind, randomized, controlled study designed to investigate the ability of supplemental perioperative oxygen to reduce wound infection. Participants were age 18 to 80 years, had no coexisting serious medical conditions, and were scheduled to undergo elective colorectal surgery at one of 14 participating hospitals in Spain. No patients undergoing minor or laparoscopic surgery were included. Anesthesia and antibiotic prophylaxis were standardized for the study. Patients were randomized by computer-generated codes to receive an oxygen/air mixture of 30% or 80% fraction of inspired oxygen ($F10_2$) intraoperatively and postoperatively for 6 hours. After 6 hours, oxygen was given only in amounts needed to maintain 92% saturation. Postoperative care was determined by the attending surgeon who was unaware of the patient's oxygen group.

Wounds were inspected daily and surgical site infections (SSI) were diagnosed according to the definitions of the Centers for Disease Control and Prevention. Infections occurring during the first 14 days were considered for analysis.

Nine patients did not meet inclusion criteria. Of the remaining 291 patients, 143 received 30% and 148 received 80% oxygen. The 2 groups were similar in clinical characteristics, including preoperative laboratory studies and risk of infection score. Surgical characteristics, including length of operative procedure, blood loss, and transfusion rate, were also similar between the 2 groups.

Fifty-seven patients (19.3%) developed a wound infection. The incidence of wound infection was 35 of 143 (24%) in the 30% $F10_2$ group and 22 of 148 (14.9%) in the 80% $F10_2$ patients ($P = 0.04$). The risk of SSI was 39% lower in the high oxygen group compared with those who received less oxygen (relative risk, 0.61; 95% confidence interval [CI], 0.38–0.98). Other measures of surgical outcome, including return of bowel function, ability to tolerate solid food, ambulation, suture removal, and duration of hospitalization, were not significantly different for the 2 treatment groups. When patients who developed wound infections were compared with those without infection, the group with SSI had a longer time to ambulation (mean, 4.9 vs 3.9 days; $P = 0.008$), a longer time to staple removal (11.6 vs 10.1 days; $P = 0.007$), and were in the hospital longer (15.1 vs 10.7 days; $P = 0.001$).

Two patients, both in the 30% oxygen group, died of sepsis during the study period. After multivariate analysis of possible confounding variables, the relative risk of wound infection in patients who received 80% oxygen was 0.46 (95% CI, 0.22–0.95; $P = 0.04$) compared with those who received 30% oxygen.

EDITORIAL COMMENT

(In the United States these days, surgical wound infection occurs after less than 1% of abdominal or vaginal hysterectomies. This is a marked reduction in the last 20 years brought about largely because of prophylactic antibiotics. More than 25 prospective, randomized studies have shown the effectiveness of prophylactic antibiotics in reducing postoperative infections with either abdom-

inal or vaginal hysterectomy. In a recent study of antibiotic prophylaxis in Medicare recipients from all 50 states undergoing a variety of surgical procedures, Bratzler et al found that 90% of 2395 women who underwent a hysterectomy in 2001 received prophylactic antibiotics as recommended by accepted protocols (Arch Surg 2005; 140:174). However, only 54% received their antibiotics within an hour of the incision time. It is not clear exactly what the effective time interval is for prophylactic antibiotics for hysterectomy. For example, the half-life of Mefoxin is approximately 1 hour so that doses given more than 2 hours before surgery may not be effective. However, cefotetan has a plasma half-life of 3 to 4.6 hours so it would be expected to be effective if administered even 2 hours before the incision for an average hysterectomy. To maintain good tissue levels of antibiotics during surgery, it is recommended that a second dose of the prophylactic antibiotic be given if the surgical procedure lasts longer than twice the half-life of the antibiotic. Significant blood loss, which "washes out" the antibiotic, would be another indication for redosing the drug. There is no proven benefit to continuing the antibiotics after the incision is closed in a patient in whom gross contamination during surgery has not occurred.

Can increased levels of inspired oxygen during surgery and in the immediate postoperative period further decrease the incidence of surgical wound infection? The study abstracted here suggests that increasing the fraction of inspired oxygen (FIO_2) from the standard 30% to 80% during general anesthesia and for the next 6 hours significantly decreases wound infection by 9% (from 24–15%) in patients undergoing colorectal surgery. However, in another prospective, randomized, double-blind series of 165 patients from Cornell Medical College in New York, Pryor et al found exactly opposite results (JAMA 2004;291:79)! Their patients included some gynecologic oncology patients undergoing radical debulking surgery, and colorectal resection was not required for study entry. They found that the patients given an increased FIO_2 of 80% had a 25% wound infection rate compared with 11.3% in patients managed with a standard 30% FIO_2 ($P = 0.02$). In a third recent similar study, Grief et al prospectively randomized 500 patients undergoing elective colorectal resection at several academic centers in the United States and abroad and found a significantly decreased rate of surgical wound infections in the 80% FIO_2 group (5.2% vs 11.2%, $P = 0.01$) (N Engl J Med 2000;342:161). Although there are some differences in the study design and patient eligibility between the studies, these surprising differences in results force us to conclude that increasing the FIO_2 in the perioperative period has not yet been proven to decrease the risk of postoperative surgical site infection. This practice cannot be recommended for routine hysterectomy in which the risk of wound infection is already much lower than for patients undergoing colorectal surgery.—HWJ)

Mode of Delivery and Severe Stress Incontinence: A Cross Sectional Study Among 2625 Perimenopausal Women

Xavier Fritel, Virginie Ringa, Noëlle Varnoux, Arnoud Fauconnier, Stéphanie Piault, and Gérard Bréart

INSERM Unité 149 (Unité de Recherches Épidémiologiques en Santé Périnatate et Santé Des Femmes), Villejuif Cedex, France

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ABSTRACT

The authors conducted a questionnaire-based survey of urinary stress incontinence (USI) and related obstetric risk factors in perimenopausal women. The 3114 female members of the French GAZEL epidemiologic study who were 45 to 50 years old between 1990 and 1996 were sent a questionnaire about urinary stress symptoms and their obstetric history.

There were 2625 responses with sufficient information for analysis. The cohort members who returned the survey were more likely to have a high school education than those who did not respond, but there were no differences in age, body mass index (BMI), parity, marital status, or smoking ($P = 0.01$ for education).

Eight hundred twenty-nine women (32%) reported no USI symptoms in the 4 weeks before completing the survey, 1410 (54%) experienced symptoms "occasionally" or "sometimes," and 386 (15%) reported severe USI with frequent or constant symptoms. Most of these women (300 of 386, 77%) considered their symptoms to be a significant problem. Nearly half (186, 46%) of the women with severe USI said that they wore pads for protection, and 241 (62%) indicated that they wanted treatment for this problem. Two hundred forty-one (62%) had discussed treatment options with their physician and 147 (38%) had prior unsuccessful treatment for USI.

There were no differences in severe USI symptoms between women who had vaginal deliveries and those who underwent cesarean sections. The severity of USI increased with increasing parity. Multivariate analysis of possible risk factors, including BMI, history of diabetes, previous hysterectomy, surgical treatment of incontinence or pelvic organ prolapse, parity, age at first delivery, and mode of first and subsequent deliveries, was performed for the entire study population. After analysis, BMI greater than 30 kg/m^2, history of diabetes, and previous urinary incontinence surgery were all associated with an increased risk of USI. Parous women were at higher risk for USI than nulliparous women, but the number of deliveries was not significant.

When parous women only were considered in logistic regression analysis of risk factors for USI, including BMI, diabetes, previous incontinence surgery, age at first delivery, and mode of delivery, only age less than 22 years of age at first delivery was found to be predictive of USI.

EDITORIAL COMMENT

(One of the strong arguments put forward in favor of elective cesarean delivery is that it will decrease trauma to the pelvic floor and, thus, reduce the risk of stress urinary incontinence in later life. In a very large questionnaire study from Norway, Rortveit et al found that the risk of stress urinary incontinence was significantly higher in women who had only vaginal deliveries compared with those who were delivered only by cesarean section (N Engl J Med 2003;348: 900). The reported prevalence of stress incontinence among women who had no deliveries was 4.7%, whereas those women who had all deliveries by cesarean section was 7.0% and 14.7% of the women who had all vaginal deliveries reported stress incontinence. The differences were most striking among younger women, and the prevalence of all types of incontinence increased in older women. In the 50- to 65-year-old age group, overall incontinence rates were similar for the cesarean and the vaginal delivery groups, 28.6% and 30%, respectively.

The age of the patients in the study may be the reason why some studies have found urinary

incontinence to be increased after vaginal delivery, whereas other studies, including the one abstracted here, have not. The average age of women in the Norwegian study was approximately 38 whereas, in the French study abstracted here, the average age of the women was approximately 55. The prevalence of urinary incontinence increases with age, but the increased risk of urinary incontinence, especially stress incontinence associated with obstetric delivery, is most pronounced in women in their 20s and 30s. After age 40, the prevalence of urinary incontinence increases among all risk groups so that the significance of mode of delivery, which was observed in the younger population, is no longer a significant risk factor.

The importance of age and loss of estrogen effect on the pelvic support tissues is so important that many of the risk factors for urinary incontinence that have been reported in younger populations are no longer significant in older women. These include obesity, parity, race, medical comorbidities, including diabetes, and smoking, all of which have been reported to be associated with the risk of urinary incontinence (Melville et al. Arch Intern Med 2005;165:537).

We might, therefore, conclude that abdominal versus vaginal delivery might be expected to reduce a woman's risk of developing moderate or severe symptoms of urinary incontinence from 8% to 10% to approximately 5% during the 30- to 50-year age span. After age 50, significant urinary incontinence is reported by 40% or more of U.S. women, and there is little difference in the various risk groups in these postmenopausal women.—HWJ)

Resource Utilization for Cancer Patients at the End of Life: How Much Is Too Much?

Sharyn N. Lewin, Barbara M. Buttin, Matthew A. Powell, Randall K. Gibb, Janet S. Rader, David B. Mutch, and Thomas J. Herzog

Division of Gynecology Oncology, Washington University School of Medicine, St. Louis, Missouri; and Division of Gynecologic Oncology, Columbia University School of Physicians and Surgeons, New York, NY

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ABSTRACT

This paper presents a comparison of total hospital costs for the final 60 days of life for patients with ovarian cancer managed by hospice versus those who did not receive hospice care. The study subjects were 84 women who had been treated at the Barnes-Jewish Hospital for ovarian cancer who died from their disease between 1999 and 2003. Clinical and financial data were obtained from a review of the medical records of these patients.

Seventeen patients (20%) were enrolled in hospice care for more than 10 of their final 60 days. These comprised the hospice group. The nonhospice group included 67 (80%) women who received hospice care for 10 or fewer days. There were no significant differences in demographic or disease characteristics between the 2 groups.

During the final 2 months of life, nonhospice patients spent an average of 11.2 days (range, 0–40 days) in the hospital compared with 3.6 days (range, 0–23) for women managed in the hospice program ($P = 0.005$). In addition, 12 of the 67 women in the nonhospice group spent 1 to 22 days in the intensive care unit (ICU), whereas no hospice patients were admitted to the ICU during this time. Only one hospice patient was operated on during the final 60 days compared with 16 nonhospice patients. There were no significant differences between the 2 groups in numbers of clinic visits, chemotherapy appointments, or office visits.

The average cost per day for the final 60 days of life was $969 for women in the nonhospice group compared with $333 for women in the hospice group ($P = 0.0011$). Total hospital costs per patient, including inpatient care, ancillary services, radiology, laboratory, pharmacy, and outpatient services, were $59,319 for nonhospice patients and $15,164 for hospice

patients. In all categories, the costs were significantly greater for nonhospice patients compared with hospice patients. The per-patient cost of inpatient care for nonhospice patients was $6584 versus $1629 for hospice patients ($P = 0.0007$), and the cost of inpatient ancillary services was higher by a factor of 10 $6956 versus $596 ($P < 0.0001$). Laboratory costs per patient were $12,281 (range, $0–119,165) versus $2036 (range, $0–13,637) ($P = 0.0004$), pharmacy services were $13,650 versus $4465 ($P = 0.0017$), and radiology costs were $6063 for nonhospice versus $2343 ($P = 0.003$) for hospice patients. Per-patient outpatient services cost $7854 for the nonhospice and $3334 for the hospice group ($P = 0.033$).

Pharmacy charges for the nonhospice patients were significantly higher as a result of the cost of chemotherapy. Forty-five women (67%) of the nonhospice group received chemotherapy during their last 60 days of life compared with only 5 patients (7%) in the hospice group. However, the charges for chemotherapy accounted for only 10% of the overall cost of care during the final 60 days.

The total cost per patient during the last 2 months of life varied enormously from one physician to another from a low of $34,677 per physician per patient to a high of $112,707 per physician per patient ($P = 0.04$).

There was no significant difference in overall survival between nonhospice and hospice patients, although mean survival of the hospice patients was 40.8 months compared with 32.4 months for the nonhospice patients.

EDITORIAL COMMENT

(Although the 5-year survival rate for ovarian cancer has increased from approximately 37% to approximately 43% over the past 2 decades, the great majority of these women will have recurrent disease and die. Newer chemotherapeutic drugs, agents to support red cell and white cell proliferation, better antiemetics, long-term, easy-access intravenous lines, and minimally invasive techniques for management of effusions and placement of gastrotomy tubes, and so on, have all contributed to our ability to keep these patients alive and, in many cases, 4-, 5-, or 6-year survivals with a good quality of life are not unusual. When these remarkable interventions have been successful on several occasions allowing women with recurrent ovarian cancer to return to a seminormal quality of life, the patients, their families, and, occasionally, even the physician begin to think that there is no end to the miraculous medical interventions we can deliver. Such a goal is obviously unrealistic; this excellent paper from Washington University and Columbia reminds us that end-of-life care is very expensive, and both quality and length of survival may not be enhanced by more chemotherapy and more hospitalization.

In this study, mean survival was actually 8 months longer in the hospice group of patients who also had significantly less chemotherapy and fewer hospitalized days than the more aggressively managed patients. During the last 60 days of life, total inpatient and outpatient costs were approximately $67,173 for the nonhospice patients. Interestingly, there was a remarkable difference in the cost of care from one physician to another (a high of $112,707 per patient compared with a low of $34,677 per patient). This needs more study. Is it related to experience, training, or personal philosophy? I would also point out that this and other similar studies are not randomized in any way so we cannot assume that the hospice and nonhospice patients are completely comparable.

Only 20% of these women who died from ovarian cancer while being managed at academic medical centers received more than 10 days of hospice care. With the apparent futility of aggressive management and the advantage of hospice in the last few months of life, why are not more patients effectively encouraged to use at-home palliative hospice care? Cost arguments are good only for healthcare policy analysts. Although most physicians want to help reduce national healthcare costs, in discussions with individual patients and their families, cost must always be secondary to quality of care, which is the main reason we choose this or that treatment approach. As a matter of fact, although home hospice care consumes less measurable healthcare resources, it may well be more expensive in dollars and lost productivity for the family caregivers. Bed linens, extension cords, humidifiers, and food for the caregivers all come out of pocket, not to mention time off from work. Despite these often unmeasured expenses, most patients and their families greatly appreciate the closeness that hospice home care provides in the last weeks or months for patients. We are very fortunate also

to have an inpatient hospice facility in Nashville for these patients where home care in the last few weeks is not appropriate.

When is it time to stop all the cancer-directed therapy and switch to emphasis on comfort care? This is always a very hard question, but one which the physician needs to introduce after the second- or third-line chemotherapy. In a nice study of the clinical course of disease over the last year of life in women with ovarian cancer, von Gruenigen et al found that admissions for bowel obstruction, pleural effusion, or ascites were indicators that further chemotherapy was ineffective (Gynecol Oncol 2003;90:619). Attempted surgery to relieve or bypass bowel obstruction is controversial and requires considerable judgment on the part of the surgeon. It is rarely palliative in women with extensive intraabdominal cancer who have received multiple courses of chemotherapy. Counseling, emotional support, and palliative measures, including pain medication, antiemetics, and antidepressants, are often the best things we can do for these women with advanced ovarian cancer.—HWJ)

Squamous Vulvar Intraepithelial Neoplasia: 2004 Modified Terminology, ISSVD Vulvar Oncology Subcommittee

Mario Sideri, Ronald W. Jones, Edward J. Wilkinson, Mario Preti, Debra S. Heller, James Scurry, Hope Haefner, and Sallie Neill

European Institute of Oncology, Milan, Italy; National Women's Hospital, Auckland, New Zealand; Department of Pathology, Immunology and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, Florida; Department of Obstetrics and Gynecology, University of Turin, Turin, Italy; University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey; Hunter Regional Medical Center, Nexpath, New South Wales, Australia; Department of Obstetrics and Gynecology, University of Michigan Hospitals, Ann Arbor, Michigan; and St. John's Dermatology Centre, St. Thomas Hospital, London, U.K.

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ABSTRACT

The terminology for squamous vulvar intraepithelial neoplasia (VIN) was established in 1986 by the International Society for the Study of Vulvar Disease (ISSVD). In this classification, abnormal changes in vulvar tissue seen on cytology are categorized as VIN 1, VIN 2, or VIN 3. Although the grading is similar to that used for cervical intraepithelial lesions (CIN), there is no evidence that VIN and CIN have a similar natural history or that the grading of VIN represents a biologic continuum.

It is now accepted that VIN 1 has a low malignant potential and is not a precursor to VIN 2 or 3. As originally described, VIN 1 denotes basally cellular changes in the basal epithelial that are relatively uncommon and are an effect of exposure to human papillomavirus (HPV). Its diagnosis varies from pathologist to pathologist and is not reproducible.

The categories of VIN 2 and VIN 3 have been useful in describing high-grade disease, but they do not differentiate between lesions usually associated with high-risk HPV types (VIN, usual type) and other lesions not resulting from exposure to HPV (VIN, differentiated).

The ISSVD proposal for vulvar intraepithelial neoplasia uses the term VIN for all high-grade squamous lesions. Two different categories of VIN are to be used VIN, usual type, is related to HPV. It is further subdivided into 3 histologic subtypes: warty, basaloid, and mixed. These lesions are unifocal or multifocal and may present clinically as patches, erosion, plaques, papules, and nodules with hyperkeratotic, verrucous, pigmented red or white changes. The progression of VIN, usual type, to invasive cancer in untreated patients has been unequivocally demonstrated, especially in women

over 30 years of age or immunocompromised women. A variant of VIN, usual type, associated with genital warts or pregnancy is seen in some younger women and can regress spontaneously.

VIN, differentiated type, is not associated with HPV and is related to lichen sclerosa and/or squamous cell hyperplasia. It is a less common diagnosis usually seen in older women. It usually presents as a warty papule or hyperkeratotic plaque. It is commonly seen during follow up of women who have been treated for lichen sclerosus or invasive vulvar cancer.

Rarely, a pagetoid type of VIN is seen that cannot be classified as either VIN, usual type, or VIN, differentiated type. This type of VIN can be termed VIN, unclassified.

EDITORIAL COMMENT

(In 1986, The International Society for the Study of Vulvar Disease (ISSVD) proposed a classification for vulvar intraepithelial neoplasia (VIN) (J Reprod Med 1986;31:973). Although the terminology of VIN 1, 2, and 3 was similar to the widely used terminology for cervical intraepithelial neoplasia—CIN 1, 2, and 3—the experts were careful to point out that the natural history of VIN has not been well studied, and it should not be assumed that VIN will behave or should be managed in the same way as CIN.

As more evidence is accumulated, including the very large series with long follow up from New Zealand discussed in this issue of the *Survey*, a clearer picture of the natural history of VIN has led to a new classification. There are 2 main changes in this new terminology that are important for the clinician. First, VIN 1, low-grade or mild vulvar dysplasia, should no longer be used. Similar to CIN, these minimal epithelial abnormalities are often transient and regress in 6 to 18 months with no long-term sequelae. They are often associated with human papillomavirus (HPV) and are most commonly seen in relatively young women. Because these minor lesions do not usually progress to invasive vulvar cancer and they do not require active treatment, they should not be considered in the same continuum of VIN, which implies a certain malignant potential. It is suggested that these minor histologic changes be described as "flat condyloma acuminatum" or HPV effect. The use of the term atypia is discouraged.

The new VIN terminology applies only to high-grade abnormalities and folds together the older VIN 2 and 3 lesions into the single all-encompassing term VIN. I would suggest that until this new terminology becomes clear to both the clinician and the pathologists that the term high-grade VIN be used to emphasize and clarify the diagnosis (Table 1).

The second major change in the new terminology for VIN is related to the morphology and etiology of the lesions. VIN is divided into 3 subgroups based on whether the lesion is HPV-related or not. In general, the "usual type" is more common, it tends to be seen in young women, and it is associated with HPV. It may be multifocal. It has several morphologic types, which are classified as warty, basaloid, or mixed. The other main subtype is designated VIN, "differentiated type". These lesions are not HPV-related. They tend to occur in older women and are unifocal. It is commonly seen on the vulva in women who have previously been treated for invasive squamous cell carcinoma of the vulva or in association with lichen sclerosus.

All of these histologic subtypes have malignant potential and should be adequately sampled; in most cases, they should be excised or destroyed as discussed in the note on the following article by Ron Jones.—HWJ)

TABLE 1
Squamous vulvar intraepithelial neoplasia (VIN) terminology (ISSVD, 2004)

VIN, Usual Type	VIN, Differentiated Type	VIN, Unclassified Type
VIN, warty type		Not fitting either usual or differentiated types
VIN, basaloid type		Rare VIN of pagetoid type
VIN, mixed (warty/basaloid)		

Vulvar Intraepithelial Neoplasia: Aspects of the Natural History and Outcome in 405 Women

Ronald Jones, Darion M. Rowan, and Alistair W. Stewart

Vulvar Clinic, Department of Gynecology, National Women's Hospital, Auckland, New Zealand; and Section of Epidemiology and Biostatistics, School of Population Health, University of Auckland, Auckland, New Zealand

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ABSTRACT

From 1962 to 2003, 405 women with vulvar intraepithelial neoplasia (VIN) 2–3 were seen in the vulvar clinic of the National Women's Hospital in Auckland, New Zealand. This paper presents an analysis of the clinical characteristics and outcomes after surgical treatment of this series of patients. A few women received no treatment, and the clinical course of their disease is also presented.

All diagnoses were made according to the histologic criteria and revised terminology of the International Society of Vulvovaginal Disease. All patients had histologically diagnosed VIN. To avoid including women with unidentified invasive cancer, women with an original diagnosis of VIN who were subsequently diagnosed with invasive vulvar cancer within 1 year were excluded.

From 1962 to 1979, the mean age of patients in this series was 50 years; since 1980, the mean age has dropped to 39 years with 79% of patients under 50 years of age at the time of diagnosis. The ethnic background of the 405 women corresponded to contemporary ethnic populations. Eighty-four percent of patients were smokers at the time of diagnosis. One hundred seventy-three women had a history of some form of sexually transmitted infection, including 138 (34%) with genital condyloma. Five patients were positive for human immunodeficiency virus. A history of treatment for cervical intraepithelial neoplasia 2 or 3 was obtained from 112 patients, and 17 had been treated for vaginal intraepithelial neoplasia. Another 17 women had been treated for cervical invasive cancer. Twenty-six patients were taking immunosuppressive medication. Over 80% of women were symptomatic at the time of diagnosis. One half had a lesion involving the perineum and perianal region.

The follow-up period was more than 5 years for 215 patients and more than 10 years for 102. Half of all patients required a second treatment for VIN by 13.7 years, but most recurrences were in the first 5 years. Recurrent disease was more likely in women over 30 years of age (92 of 256; 36%) than in women less than 30 years of age (30 of 126; 24%) ($P = 0.014$). Initial treatments were most often surgical excision ($n = 196$) or laser vaporization ($n = 118$), but 5-fluoruracil and imiquimod were also used. Similar percentages of patients treated by surgical excision or laser vaporization had a recurrence of disease within 5 years of initial treatment (34% and 39%, respectively). The risk of recurrence within 5 years estimated to be over 50% for patients with positive surgical margins and 15% for patients with negative margins.

There were 63 women who received no treatment. The lesion regressed before treatment could begin in 47 patients and progressed to invasion before treatment in 10 patients. In addition, 5 very young patients are being followed with the expectation that the lesion will spontaneously regress, and one woman, who has a slowly increasing area of white plaque over the vulvar skin, has consistently refused treatment for over 20 years.

Twenty-seven women, of whom 17 were treated with surgical excision or laser vaporization and 10 were "untreated" (received only diagnostic biopsy or partial excision), have developed squamous cell carcinoma of the vulva or perianal area more than 1 year from their diagnosis. Of the 17 women who developed invasive carcinoma of the vulva, perianus, or urethra, 10 had been treated for VIN more than once, including 3 with 4 or more previous treatments. Three had carcinoma develop in more than one area.

Nine of the 17 women who developed invasive disease had positive histologic margins and were considered treatment failures. The median disease-free interval for these patients was 2.4 years (range, 1.1–7 years). The remaining 8 women who were subsequently diagnosed with invasive vulvar disease seemed to have new cancers arising in the "field" of the previous lesion. The median disease-free interval for these patients was 13.5 years (range, 3–16 years).

Invasive cancer developed in 10 women with untreated VIN, 5 of which occurred in the early years of this study when no treatment was the policy. The remaining 5 were untreated because of comorbid conditions or physician or patient preference.

Five women were considered to be strong candidates for spontaneous regression of disease. They were all under 25 years of age and had small, popular pigmented lesions. These patients are currently under observation with the expectation that these lesions will regress.

EDITORIAL COMMENT

(There should be no doubt about the malignant potential of vulvar intraepithelial neoplasia (VIN). At the recent World Congress of the International Federation for Cervical Pathology and Colposcopy, Ron Jones, the lead author of this study, presented the very compelling scientific and human story of the "tragic experiment" in which a number of New Zealand women with carcinoma in situ of the cervix and vulva were observed with no treatment in an attempt to prove that these were not precursors of invasive cancer. As we now know, this "experiment" proved just the opposite—much to the detriment of the women involved.

Even with treatment, many patients with VIN recur and some will develop invasive cancer. In this very large series with a long follow up, 17 women (3.8%) developed invasive vulvar, perianal, or periurethral cancer more than 1 year after treatment for VIN. This is very similar to a literature review by von Seters et al in which they reported a 3.3% incidence of invasive cancer after treatment for VIN (Gynecol Oncol 2005;97:645).

Recurrent intraepithelial neoplasia is far more common. With a follow up of up to 40 years, 50% of the 405 women in this series needed at least one more treatment for persistent or new VIN. Although this is a higher rate of recurrence than reported in most series, follow up is longer and more complete than in other reports. It is also interesting to note that, as with the invasive cancers reported in this series, there seem to be 2 distinct groups of patients who require retreatment: 1) women diagnosed with VIN within 2 years of the original treatment who probably have persistent disease and 2) another group of women who are diagnosed at 4 to 5 years or more who probably have new areas of VIN. For invasive cancer, the time intervals are a median of 2.4 years for women who progressed from their original VIN, whereas patients who were apparently originally cured but developed a new focus of disease that progressed to invasive cancer were diagnosed a median of 13.5 years after their original treatment.

In this series, the surgical resection margin was significantly related to the risk of requiring retreatment for persistent/recurrent disease. Positive margins were found in 47% of the women treated with excision, and they had a 50% risk of requiring retreatment in the next 5 years. On the other hand, women with negative margins had only a 15% risk of retreatment. Although this observation would seem to be intuitively true, many studies have not found positive margins a risk factor for persistent/recurrent VIN. In a series of 95 women with VIN 3 treated with surgical excision, McNally et al from Melbourne reported that "positive surgical margins were not found to be significant predictors of recurrence" (Int J Gynecol Cancer 2002;12:490). However, "uncertain" margins were recorded in almost half (42) of these women, and only 6 patients were listed as having uninvolved margins. This illustrates some of the problems with the margin controversy. It is hard to exhaustively examine the long margins of these specimens in a nonresearch setting and the lesions are often multifocal. It seems reasonable to try to obtain negative margins without extensive, disfiguring surgery, which can cause scarring and dyspareunia. Jones says that they will occasionally perform an EUA with extensive "mapping" biopsies to try to establish the extent of the lesion as a guide for definitive excision at a later date. They also found that CO_2 laser vaporization was an effective treatment modality.

This paper has many interesting findings, which are too numerous to comment on in this note. If you manage women with VIN, I urge you to review the full paper.—HWJ)

Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening

Etta D. Pisano, Constantine Gatsonis, Edward Hendrick, Martin Yaffe, Janet K. Baum, Suddhasatta Acharyya, Emily F. Conant, Laurie L. Fajardo, Lawrence Bassett, Carl D'Orsi, Roberta Jong, and Murray Rebner for the Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group

Departments of Radiology and Biomedical Engineering, Biomedical Research Imaging Center, and Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Center for Statistical Sciences, Brown University, Providence, Rhode Island; Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; Departments of Medical Imaging and Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Department of Radiology, University of Pennsylvania Medical School, Philadelphia, Pennsylvania; Department of Radiology, University of Iowa, Iowa City, Iowa; Department of Radiology, University of California at Los Angeles, Los Angeles, California; Department of Radiology, Emory University, Atlanta, Georgia; and Department of Radiology, William Beaumont Hospital, Royal Oak, Michigan

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ABSTRACT

Previous trials, limited in many respects, have not found digital mammography to be significantly more accurate than the standard film method. A total of 42,760 asymptomatic women seen at 33 sites in the United States and Canada requested screening mammography and underwent both film and digital examinations. Two radiologists independently interpreted the film and digital mammograms. All participants either had breast biopsy within 15 months after evaluation or had a follow-up mammogram 10 months or longer after entry to the study. The results were assessed by receiver operating characteristic analysis.

Both digital and film mammograms were positive in 0.5% of women. Another 2.2% had only a positive digital study, whereas 1.9% had only a positive film study. In the remaining women, approximately 95% of the total, both imaging studies were negative. Of 335 breast cancers diagnosed within 455 days after entry to the study, approximately three fourths were found within a year after evaluation. There were no substantial differences between the digital and film findings with respect to histology or stage of disease. The area under the curve was similar for the 2 studies and was not influenced by race or the risk of breast cancer. Digital mammography did, however, perform significantly better than the film method in women less than 50 years of age, in those having heterogeneously dense or very dense breasts, and premenopausal or perimenopausal women. The digital and film methods performed equally well in women age 50 years and older, those with fatty breasts or scattered fibroglandular densities, and those who were postmenopausal.

EDITORIAL COMMENT

EDITOR'S NOTE: See the combined discussion after the following abstract.

Effect of Screening and Adjuvant Therapy on Mortality From Breast Cancer

Donald A. Berry, Kathleen A. Cronin, Sylvia Plevritis, Dennis G. Fryback, Lauren Clarke, Marvin Zelen, Jeanne S. Mandelblatt, Andrei Y. Yakovlev, J. Dik F. Habbema, and Eric Feuer for the Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators

M. D. Anderson Cancer Center, Houston, Texas; National Cancer Institute, Bethesda, Maryland; Stanford University, Stanford, California; University of Wisconsin–Madison, Madison, Wisconsin; Cornerstone Systems, Lynden, Washington; Dana-Farber Cancer Institute, Boston, Massachusetts; Georgetown University, Washington, DC; University of Rochester, Rochester, New York; and Erasmus University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

In several countries, a drop in mortality from breast cancer has been documented starting in 1975. Both early detection by mammographic screening and advances in management are plausible explanations. The National Institutes of Health have used a competitive peer review process to develop 7 independent statistical models of breast cancer incidence and mortality. A consortium of investigators used the same sources to obtain data on screening mammography, adjuvant treatment, and health benefits relating to the rate of death from breast cancer in the years 1975–2000.

The use of mammographic screening in women age 40 and over increased markedly over the period 1985 to 2000. The use of adjuvant treatment depended on numerous factors beside the calendar year, including age, tumor stage, and estrogen-receptor status. The proportion of women given adjuvant treatment increased from virtually none in 1975 to approximately 80% in 2000. By 2000, half of all women were using tamoxifen. All 7 models predicted similar proportional reductions in mortality from a combination of screening and adjuvant therapy. The proportion of overall reduction in breast cancer deaths ascribed to screening ranged from 28% to 65% (median, 46%). The remaining decrease in mortality was associated with adjuvant treatment. Variation between models in the absolute contribution of screening was greater than for treatment. Combined screening and adjuvant therapy reduced breast cancer mortality by 25 to 38% (median, 30%). The proportion of decreased mortality ascribed to adjuvant treatment was 12 to 21% (median, 19%). For each of the 7 models, the combination of screening and adjuvant treatment lowered mortality slightly less than the sum of contributions from screening and adjuvant therapy alone.

The investigators conclude from these findings that both mammographic screening and adjuvant treatment have helped to lower deaths from breast cancer in the United States.

EDITORIAL COMMENT

(These 2 studies, in the same issue of the *New England Journal of Medicine*, confirm the value of screening mammography in detecting breast cancer and reducing the risk of death from this common neoplasm in U.S. women. The first article by Pisano et al compares the relative value of film versus digital mammography, whereas the article by Berry et al analyzes the benefits of screening mammography and adjuvant therapy in reducing breast cancer risk.

In the study by Pisano et al, although the diagnostic accuracy of film and digital mammography was similar overall, the accuracy of digital mammography was significantly better than that of film mammography among women under the age of 50 years, women with heterogeneously dense or extremely dense breasts on mammography, and premenopausal and perimenopausal women.

Readers may recall the sometimes vociferous comments, many based on Canadian data, that mammography was not warranted in women between the ages of 40 and 50 years. Also, of course, this is one of the groups in which digital mammography outperformed film mammography, as found in the present study by Pisano et al.

Indeed, there were, and still are, some critics who feel that there is little point in performing mammograms at all. However, most experts seem to agree that mammography reduces the death rate in women who are 40 years of age or older (eg, Humphrey LL et al. Ann Intern Med 2002;137:347 and the second article in this present review by Berry et al).

Our readers also know that dense breast tissue makes accurate mammographic interpretation more difficult, and again, this is another group of women in whom digital mammography appears to be more accurate in the present article by Pisano and colleagues. Breast density tends to be greater in younger women, particularly those taking oral contraceptives and postmenopausal women receiving hormone therapy (HT).

What are some of the other putative advantages of digital mammography? 1) There is easier access to images and computer-assisted diagnosis; 2) improved transmission, retrieval, and storage of images; 3) use of a lower average dose of radiation without compromising diagnostic accuracy; and 4) digital imaging permits the elimination of film processing, storage, copying and retrieval. (As D. David Dershaw, in an editorial in this issue of the *New England Journal of Medicine* [2005;353: 1846] about these 2 articles notes, "Digital-image manipulation makes it possible to place images in a window, level them, and electronically magnify-features that allow images to be evaluated without the need to repeat mammography. With digital imaging, other advantages are real-time interpretation of mammograms at distant sites with the use of teleradiology and computer-aided detection equipment.")

So what are the disadvantages of digital mammography? Certainly, cost is a factor, and Dr. Dershaw estimates that digital imaging systems are often 1[1/2] to 4 times as expensive as film mammography systems. Additionally, women with large breasts who undergo digital mammography may require multiple exposures to ionizing radiation, because the smaller imaging size requires the acquisition of multiple images to image the breasts completely. Thus, the final verdict is not completely in. However, in the approximately 8% of the facilities in the United States and similar systems abroad that have digital imaging capacity, the use of digital imaging in the subgroups in which digital mammograms appear to offer greater accuracy, they seem a worthwhile alternative. In the second study by Berry et al, the authors used a variety of modeling techniques to assess relative and absolute contributions of screening mammography and adjuvant treatment in reduction in breast cancer mortality from 1975 to 2000.

In the study, a consortium of investigators developed 7 independent statistical models of breast cancer incidence and mortality. The various groups used the same datasets regarding use of screening mammography, adjuvant treatment, and benefits of treatment related to the rate of death from breast cancer. They found that the proportion of this total reduction to screening varied in the 7 models from 28% to 65% (median, 46%) with adjuvant therapy contributing the rest. They also found that the variability across models in the absolute contribution of screening to the decrease in mortality was greater than it was for adjuvant treatment. Interestingly, the percentage of women who received chemotherapy in 1975 was almost nil for node-positive stage II or IIIA disease and rose to approximately 80% by 2000, very likely responsible for a substantial part of the decreases in mortality by 2000.

Analyzing the data from the 7 models, the estimated rate of death from breast cancer in the absence of screening and adjuvant therapy would have increased by approximately 30% from 1975 to 2000 modeled on the background trend in the absence of screening.

In essence, the 7 models, using common sources of data but with different approaches and assumptions, all concluded that screening and treatment both contributed to the observed decline in the rate of death from breast cancer, and that the decline was a reflection of a combination of screening and therapy and not by either one alone.

The conclusions from the different models seem to vindicate the use of screening mammography and adjunctive therapy. Coupled with continued improvement in treatment and the type of screening modalities described in the study of Pisano and colleagues, it is an encouraging trend. However, we obviously still have a long way to go.—RBJ)

Glucose Intolerance, Insulin Resistance and Cardiovascular Risk Factors in First Degree Relatives of Women With Polycystic Ovary Syndrome

Murat Yilmaz, Neslihan Bukan, Reyhan Ersoy, Ayhan Karakoç, Ilhan Yetkin, Göksun Ayvaz, Nuri Çakir, and Metin Arslan

Department of Endocrinology and Metabolism, Kinkkale University Faculty of Medicine, Kirikkale, Turkey; and Department of Biochemistry and Department of Endocrinology and Metabolism, Gazi University Faculty of Medicine, Ankara, Turkey

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ABSTRACT

Findings on familial aggregation of polycystic ovary syndrome (PCOS) are consistent with a genetic component. Studies have shown greater insulin resistance (IR), higher serum androgen levels, more frequent glucose tolerance disorder, and more type II diabetes in first-degree relatives of patients with PCOS. The present study examined these variables in addition to cardiovascular risk factors in 120 family members of 55 patients with PCOS. There were 40 mothers, 38 fathers, 25 sisters, and 17 brothers. The control group included 75 healthy subjects with no family history of PCOS or diabetes. The study and control groups were matched for age and body weight. Insulin resistance was estimated by homeostatic model assessment (HOMA IR), log HOMA, insulin sensitivity index, the quantitative insulin sensitivity check index (QUICKI), and the area under the curve for insulin (AUCI) during an oral glucose tolerance test.

Glucose intolerance of any degree was documented in 40% of mothers and 52% of fathers of patients with PCOS. Six cases of glucose tolerance disorder were found in control mothers and fathers (15%). First-degree relatives of patients with PCOS, compared with control subjects, had significantly higher serum levels of fasting insulin, HOMA-IR, log HOMA, and AUCI. Control subjects had significantly increased QUCKI, ISI levels. In addition, serum levels of adiponectin were significantly higher than in all subgroups of relatives of PCOS subjects. Fathers and mothers of patients with PCOS, but not brothers or sisters, had higher serum homocysteine and resistin levels. Blood lipid levels, including total cholesterol and low-density lipoprotein (LDL)-cholesterol, were significantly higher in fathers of patients with PCOS than in the control group. The opposite was the case for serum levels of high-density lipoprotein (HDL)-cholesterol and apoprotein A. Levels of total cholesterol, LDL-cholesterol, apoprotein B, and triglycerides were higher in mothers of patients with PCOS than in control subjects, but levels of HDL-cholesterol and apoprotein A were similar. Levels of most blood lipids were similar in patients' sisters than in control subjects, but brothers of patients had higher blood lipid levels than control subjects (exceptions were HDL-cholesterol and apoprotein A). Both groups of parents of patients with PCOS had higher blood pressure, but this was not true for the brothers and sisters.

These findings indicate that first-degree relatives of patients with PCOS, like the patients themselves, are at increased risk of developing cardiovascular disease (CVD). These family members should be monitored for both CVD and diabetes, and preventive measures should be taken when appropriate.

EDITORIAL COMMENT

(A friend of mine told me recently how he distinguishes between events attributable to *heredity* and those attributable to *environment*. He said that if his son looks like himself, that is *heredity*, whereas if his son looks like his neighbor, that is *environment*.

In the present study, a group of Turkish investigators sought to determine whether first-degree relatives of women with polycystic ovary syndrome (PCOS) had increased glucose intolerance, insulin resistance, and risk factors for cardiovascular disease.

I suspect that many of our readers, like me, have seen several members of the same family with various stigmata of PCOS, strongly implying that there is at least a genetic *component* of PCOS. In fact, several studies, including those by Hague et al. (Clin Endocrinol [Oxf] 1988;29:593; Legro RS et

al. Proc Natl Acad Sci U S A 1998;95:14956; and Govind A et al. J Clin Endocrinol Metab 1999;84: 38), have shown a familial aggregation of PCOS consistent with a genetic etiology.

They studied a total of 120 family members (40 mothers, 38 fathers, 25 sisters, and 17 brothers) of 55 patients with PCOS and 75 unrelated, healthy control subjects without a family history of diabetes or PCOS. They quantified insulin resistance and glucose intolerance by a variety of widely used tests, as well as serum adiponectin, resistin, homocysteine, and lipid concentrations.

In parents of the women with PCOS, 40% of the mothers and 52% of the fathers had some degree of glucose intolerance, whereas a total of only 15% of the control parents had abnormal glucose tolerance. The first-degree relatives of patients with PCOS had higher fasting serum insulin, HOMA-insulin resistance, and area under the insulin curve in all subgroups than the control subjects. In contrast, the control subjects had elevated QUCKI, insulin sensitivity indices, and serum adiponectin concentrations compared with first-degree relatives of subjects with PCOS.

Although a substantial number of studies have demonstrated the alterations in glucose metabolism in families in which PCOS was present, few have explored the cardiovascular risks in first-degree relatives of patients with PCOS, although a recent study by Kaushal et al (Clin Endocrinol [Oxf] 2004;60:322) indicated that brothers of patients with PCOS had insulin resistance and endothelial dysfunction early in life.

As I have commented in previous reviews in the *Survey*, many patients with PCOS have components of the metabolic syndrome (dyslipidemia, insulin resistance, hypertension, and obesity). Also, individuals with the metabolic syndrome, whether or not they have PCOS, are more prone to develop cardiovascular disease and type 2 diabetes.

That first-degree relatives of patients with PCOS also have an increased incidence of glucose intolerance and insulin resistance as well as cardiovascular risk factors is not too surprising. That some of the markers of cardiovascular risk factors were found in these first-degree relatives also is not too surprising. However, because there have been some discrepancies in results from different studies, it is useful to have this additional information.

Resistin is a protein found in preadipocytes that undergo differentiation into mature adipocytes. It induces insulin resistance and impaired glucose tolerance (Kim K et al. J Biol Chem 2001;276: 1152; Kershaw EE, Flier JS. J Clin Endocrinol Metab 2004;89:2548). Resistin can promote endothelial cell activation, another example of adipokinin–endothelial activation (Verma S et al. Circulation 2003;108:736). As indicated, in the present study, resistin levels were significantly elevated in the fathers and mothers of the women with PCOS.

It was somewhat surprising that markers of inflammation such as C-reactive protein, which also are associated with cardiovascular risk, were not measured. However, the various indicators of dyslipidemia studied in the present report, coupled with increased homocysteine concentrations (an independent risk factor for cardiovascular disease) and lower levels of adiponectin (an adipocyte product that I have discussed in previous reviews in the *Survey*) found to be associated with essential hypertension, cardiovascular disease, diabetes, and obesity, provides substantial data suggesting that first-degree family members are at increased risk for cardiovascular risk.

In light of these findings, the authors suggest monitoring these relatives for cardiovascular disease. It seems like a reasonable suggestion and one that should be followed by preventive measures, both in terms of lifestyle and medication, when indicated.—RBJ)

Is Expectant Management of Sonographically Benign Adnexal Cysts an Option in Selected Asymptomatic Premenopausal Women?

Juan Luis Alcázar, Gerardo Castillo, Matías Jurado, and Guillermo López Garcia

Department of Obstetrics and Gynecology, Clínica Universitaria de Navarra, School of Medicine, University of Navarra, Pamplona, Spain

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ABSTRACT

In premenopausal women, functional cysts of the ovary may regress spontaneously, whereas true benign neoplasms are likely not to regress. Whether cysts are precursors of ovarian malignancy remains uncertain. The investigators used transvaginal sonography to determine whether expectant management of sonographically benign ovarian cysts is an option for the management of women without symptoms. A total of 120 asymptomatic women seen in a 6-year period participated in this prospective longitudinal study. The women, whose mean age was 40.6 years and who ranged in age from 19 to 50 years, had a sonographically benign ovarian cyst less than 6 cm in size. Conservative management was offered and the patients were followed up at intervals of 6 to 12 months; the initial check was made 3 months after diagnosis.

Ten cysts, 8.3% of the total, disappeared after a median follow up of 42 months. The initial diagnosis was endometrioma in 3 of these cases, hemorrhagic cyst in 3, and simple cyst in 4. The median time from diagnosis to disappearance of the lesion was 34 months. Eleven women (9.2%) were lost to follow up. Only in mature teratomas was there a significant change in size during follow up. None of the women developed signs or symptoms of ovarian cancer or complications related to the adnexal mass. In no case was it felt necessary to surgically remove the mass.

These findings support a conservative approach to ovarian masses found in asymptomatic premenopausal women without symptoms, providing that transvaginal ultrasonography shows the lesion to be benign.

EDITORIAL COMMENT

(It has been drilled into me since the days of my residency that if ovarian cysts are 5 cm or greater, or if they do not resolve spontaneously, they must be dealt with surgically either by laparoscopy or laparotomy. In the present study by Alcázar et al, the authors questioned this dictum.

The authors note that although customary treatment of persistent ovarian masses is surgical removal, primarily because of malignant potential and occurrence of complications such as hemorrhage, torsion, or rupture, the natural history of ovarian masses is really not known. It is not uncommon in reproductive-age women for "functional" cysts to regress spontaneously, and the first author of the present paper, Alcázar, has demonstrated this previously (J Ultrasound Med 1997;16:819). On the other hand, true benign neoplasms will not resolve spontaneously, and whether some of these become malignant is not really known. However, as the authors note, the prevalence of ovarian cancer in premenopausal women is low (eg, Morrow CP. In: Morrow CP, Curtin JP, eds. Synopsis of Gynecologic Oncology. Philadelphia: Churchill-Livingstone, 1998: 233–280). The authors also note that transvaginal sonography is a very good method for characterizing ovarian masses and that the false-negative rate is low. Furthermore, the correlation of sonographic features with histologic findings is high in such benign tumors as endometriomas, mature teratomas, hemorrhagic cysts, peritoneal cysts, simple cysts, cystadenomas, and hydrosalpinges. Therefore, they assessed whether expectant management of sonographically benign cysts

might be an option for selected asymptomatic premenopausal women.

They performed a prospective, observational, longitudinal study in 120 women (of the 323 asymptomatic premenopausal women who had sonographically benign ovarian cysts less than 6 cm seen by them over 7 years) who volunteered to participate in a nonsurgical observational study. In all of their subjects, they performed a 3-month assessment to confirm the persistence of the cyst.

They found that the mean age of the women was 40.6 years, ranging from 19 to 50 years. With a follow up of 18 to 94 months (median, 42 months), most lesions remained unchanged in sonographic appearance and size. Ten cysts disappeared during follow up, all after more than 2 years of observation. None of their patients had development of signs or systems indicative of ovarian cancer. It should be noted that in 52 of the women, the tumor was greater than 6 cm in size and less than 6 cm in 323 women. However, although all of the 323 women with cysts smaller than 6 cm were offered conservative management initially after diagnosis, 203 underwent subsequent surgery based either on their referring physician's advice or their own decision. It was the 120 women who chose conservative management, a little less than 40% of the eligible subjects, who were studied, and 11 of these were lost to follow up. Somewhat reassuringly, none of the patients underwent surgery for the adnexal mass during follow up.

In light of the findings by Crayford et al (Lancet 2000;355:1060) that removal of benign ovarian tumors does not reduce the mortality of ovarian cancer, that a large proportion of functional cysts resolve spontaneously (Alcázar. ibid), and that there is a possibility, albeit small, of surgical complications, expectant management of sonographically benign lesions of less than 6 cm in size in asymptomatic premenopausal women probably seems warranted. An exception is mature teratomas because these do have a tendency to enlarge over time.

Finally, it should be borne in mind that the data in this study could be subject to selection bias because not all eligible women chose conservative management; whether this group would have behaved in the same manner as those who did undergo expectant management is speculative.—RBJ)

In Vitro Fertilization and Embryo Transfer in Seminatural Cycles for Patients With Ovarian Aging

Altina Castelo Branco, Nelly Achour-Frydman, Jacques Kadoch, Renato Fanchin, Gerard Tachdjian, and René Frydman

Departments of Obstetrics and Gynecology and Reproductive Medicine and Biology and Genetics of Reproduction, Hôpital Anoine Béclère, Clamart, France

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ABSTRACT

Although controlled ovarian hyperstimulation (COH) has proved more effective than in vitro fertilization (IVF) done on natural cycles, poor responses related to ovarian status defects are not rare and may account for cancellation rates as high as 24% in IVF-embryo transfer (ET) cycles. Both women with low ovarian reserve and those responding poorly to previous ovarian stimulation may be affected. This prospective study was an attempt to determine whether

seminatural cycles are a reasonable approach to patients with ovarian aging. A total of 158 cycles were monitored in 75 women. Participants were infertile women less than 38 years of age who had ovulatory cycles every 25 to 35 days and ovarian aging, defined as low ovarian reserve and characterized by high levels of follicle-stimulating hormone by cycle day 3, high estradiol and/or low inhibin B levels, and/or previous cycle cancellations because of a poor ovarian response to COH.

Up to 3 cycles were offered. The dominant follicle, selected from cycle day 8 onward, was monitored by ultrasonography and hormone measurements. When it appeared, as evidenced by a serum estradiol exceeding 100 pg/mL and a diameter of more than 12 mm, patients received a gonadotropin-releasing hormone (GnRH) antagonist followed by human menopausal gonadotropin. Oocyte pickup was done 36 hours after administration of human chorionic gonadotropin. Embryo transfers were carried out 2 days after oocyte retrieval. The luteal phase was supported by micronized progesterone.

The cancellation rate for 158 cycles was 17.7%. Oocyte pickups were done in 75.3% of cycles, and 91 mature oocytes were retrieved (57.6%). The rate of embryo transfer was 42.4%. Nineteen clinical pregnancies occurred, 5 of which resulted in spontaneous abortion. Seven of the pregnancies occurred in the first treatment cycle. The cumulative rate of pregnancy per patient after 3 treatment cycles was 35.2%.

The investigators concluded that IVF with a seminatural cycle protocol is a useful alternative to COH for those who fail to respond well. Candidates include women who require IVF, those with endocrinologic evidence of ovarian aging, and those having a history of one or 2 canceled COH cycles. Better results may be expected as the dose and duration of treatment with a GnRH antagonist are appropriately modified and as the oocyte pickup technique improves.

EDITORIAL COMMENT

(I spoke with a colleague of mine who is a member of our assisted reproductive technologies/in vitro fertilization (IVF) group about this article, and he said that one of the most frustrating problems in ovarian stimulation is the treatment of patients who are poor responders. He said that they represent anywhere from 9% to 24% of patients undergoing ovarian stimulation in various studies. He further noted that numerous different criteria have been used to characterize these patients and, unfortunately, these different definitions render comparisons between different clinical trials difficult to interpret.

Criteria used to define poor responders include the number of oocytes retrieved, the estradiol level on the day of human chorionic gonadotropin (hCG) administration or on cycle day 5, the age of the patients, and at least one canceled IVF cycle (Ubaldi FM et al. Reprod Biomed Online 2005;10:235).

My colleague also reminded me that many treatment strategies have been used to improve the outcomes in poor responders, including increasing the gonadotropin dose, adding growth hormone or corticosteroids, as well as low-dose aspirin or aromatase inhibitors, and a variety of stimulation protocols ("flare," gonadotropin- releasing hormone [GnRH] antagonists, combination of clomiphene and gonadotropins). Some authors even suggest a natural cycle with no medications.

In the present study, the authors divided the patients who were poor responders into 2 groups: 1) those who had high follicle-stimulating hormone (FSH) and estradiol on cycle day 3 and/or low inhibin B (they do not specify how many subjects had FSH and estradiol measurements only, how many had inhibin measurements only, and how many had both, nor do they provide the range of values); and 2) a poor responder group (those with normal ovarian reserve but less than 5 follicles despite adequate ovarian stimulation. (It is not clear to me why they lumped these 2 disparate groups together.)

My colleague felt that the subdivision was laudable because attempts to better understand the problem from a biologic perspective could be helpful. However, he felt that it was unclear whether this would be of help to the practicing physician.

The authors of the present study proposed the addition of human menopausal gonadotropin (hMG) and a GnRH antagonist, the "seminatural" component of the management. Treatment was not initiated until day 8, which is somewhat unusual; it is more common to begin on day 5.

Statistical analysis was performed on the 2 subgroups, which were stimulated equally with the seminatural protocol. Results were equivalent in the 2 groups and overall were not very encouraging. As my colleague noted, only 91

eggs were retrieved out of158 cycles (equivalent to 0.57 egg per cycle) and 19 clinical pregnancies per cycle were obtained (approximately 12%).

My colleague and I agreed that the major problem with this study is that there is not a control group that did not undergo the same treatment. In addition, I did not think it was optimal to have 2 GnRH antagonist protocols decided by individual clinicians with criteria for making this decision not defined.

This is an important and difficult clinical situation. Further studies of the underlying pathophysiology hopefully will lead to more efficacious treatment.—RBJ)