Aging Gracefully

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Preservation of Fertility

A comprehensive review article by Lobo in the NEJM recently[1] covers in detail the processes of fertility loss in women and potential options for the preservation of fertility. This has now become an increasingly important area of study given that the choice of delaying pregnancy has become the norm for many women in developed countries. Among some women, however, achieving pregnancy may be difficult or impossible at a later time. The ability to preserve fertility with various methods has become a key issue for some women. Lobo particularly highlights this need for women with cancer, although the same therapeutic options may be available for many other women who are reaching an advanced reproductive age. However, Lobo cautions that in the latter group, the use of the available techniques is controversial and should be considered experimental.

Aging is the most significant factor influencing the ability to conceive. In normal women, fecundity begins to decline at a more rapid pace after the age of 37.5 years. Various environmental factors and toxic exposures (such as smoking) may also affect the age of menopause. Several diseases, notably cancer, promote infertility through disease mechanism and therapy-related factors.

Tests to identify fertility problems in women analyze ovarian reserve. Decreased ovarian reserve is defined by a poor ovarian follicular response to stimulation, which by implication signifies a decreased number of oocytes. Even with normal ovulatory cycles, FSH levels may be elevated early in the menstrual cycle, signaling a decreased ovarian reserve. On day 3 of the menstrual cycle, serum FSH levels are usually less than 10mIU/ml in most assays. FSH levels that are more than 15mIU/ml on day 3 suggest a decreased ovarian reserve and a reduced probability of pregnancy; if values exceed 20mIU/ml, the probability of pregnancy is close to nil. Although these levels vary from one cycle to the next, it has been suggested that any elevation signals a poor prognosis.

Measures of estradiol that are obtained concurrently are useful, since values that are more than 80pg/ml signify disrupted folliculogenesis, which does not allow for an accurate interpretation of FSH measurements. Abnormal results of a test of ovarian reserve indicate that the probability of pregnancy is less than 5%.

Options for the preservation of fertility in patients with cancer include the removal of tissue and the aspiration of oocytes with or without stimulation with ovulation-inducing agents. After aspiration, immature oocytes may undergo in vitro maturation. Various cryopreservation techniques are also available. Ovarian transposition (ovariopexy) is used when pelvic irradiation is necessary. With the exception of ovariopexy and embryo cryopreservation performed in centers that are experienced in the techniques, the other possibilities - orthotopic transplantation and heterotopic transplantation with subsequent in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) - are considered experimental.

In all scenarios, the most successful approach is embryo cryopreservation. This technique affords a pregnancy rate of 20 to 30% per transfer of two to three embryos. However, this approach requires in vitro fertilization and a participating male partner, although frozen sperm from a donor may also be used.

Oocyte cryopreservation is another potential option. Because of the fragility of the meiotic spindle and the formation of ice crystals, the success of this approach has been limited but is improving.

Ovarian cryopreservation is an attractive approach to the preservation of fertility and has proved successful in several animal models. The rationale for this approach is that primordial follicles in excised ovarian tissue may be more resistant to freezing and thawing than are mature oocytes and may be preserved without a delay in treatment. The principal obstacle to the success of this technique is poor oocyte viability.

Another potential approach is to protect primordial follicles from chemotherapy, irradiation, or both. Pretreatment with a gonadotropin-releasing hormone agonist or antagonist to keep the ovaries quiescent during chemotherapy has been suggested but without convincing data in humans.

Although the above techniques are all options for the treatment of patients with cancer, the woman who does not have cancer but wishes merely to preserve fertility presents the greatest challenge. The cryopreservation of ovarian tissue in this setting is not warranted, and the cryopreservation of oocytes has to be considered experimental. Because embryo cryopreservation has a reasonable success rate and has been carried out for many years, it may be a reasonable approach for appropriate candidates. For all women, a final option to consider is oocyte donation. This technique affords the highest pregnancy rates, in the range of 40 to 50% per cycle.

With this technique, age is not a factor, with pregnancy possible in women in the mid-50 years, as long as the uterus remains healthy.

1. Lobo, RA. Potential Options for Preservation of Fertility in Women. N Engl J Med 2005;353:64-73.

VZV Vaccine for Older Adults

Oxman et al.[1] describe a large, randomized, double-blind, placebo-controlled trial of an investigational live attenuated zoster vaccine (derived from the Oka strain) administered to adults 60 years of age or older with the objective to boost their cell-mediated immunity against VZV, and thus decrease the incidence, severity, or both, of herpes zoster and postherpetic neuralgia.

The primary end point was the burden of illness due to herpes zoster, a measure affected by the incidence, severity, and duration of the associated pain and discomfort. The secondary end point was the incidence of postherpetic neuralgia.

From over 38,000 subjects, more than 95% continued in the study to its completion, with a median of 3.12 years of surveillance for herpes zoster. A total of 957 confirmed cases of herpes zoster (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of postherpetic neuralgia (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The use of the zoster vaccine reduced the burden of illness due to herpes zoster by 61.1% ($P<0.001$), reduced the incidence of postherpetic neuralgia by 66.5% ($P<0.001$), and reduced the incidence of herpes zoster by 51.3%($P<0.001$). Reactions at the injection site were more frequent among vaccine recipients but were generally mild. The Shingles Prevention Study Group concludes that the zoster vaccine used in this study markedly reduced morbidity from herpes zoster and postherpetic neuralgia among older adults.

The vaccine currently licensed to prevent varicella (Varivax) is at least 14 times weaker than the potency of the VZV vaccine used in this study. A preliminary study indicated that potencies of this magnitude are required to elicit a significant increase in the cell-mediated immunity to VZV among older adults - hence, the Shingles Study Group formulated a high-potency vaccine for this study. The authors comment that no study thus far has shown that the licensed varicella vaccine would be efficacious in protecting older adults from herpes zoster or postherpetic neuralgia. Thus, they do not recommend the use of the current varicella vaccine in an attempt to protect against herpes zoster and postherpetic neuralgia.

1. Oxman MN, Levin MJ, Johnson GR. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. N Engl J Med 2005;352:2271-84.

Antipsychotic Drugs and Death

This is a meta-analysis of 15 trials of atypical antipsychotics drugs marketed in the United States to treat patients with Alzheimer disease (AD) or dementia.[1] During the last decade, the newer atypical antipsychotic drugs (i.e., risperidone, olanzapine, quetiapine, and aripiprazole) have largely replaced the older conventional or first-generation antipsychotic drugs (e.g., haloperidol and thioridazine) and have been considered preferred treatments for behavioral disturbances associated with dementia. Reasons for this preference include emerging clinical trials evidence, perceived relative safety advantages compared with older antipsychotic drugs and other medications, the opinions of expert clinicians, and expectations of efficacy.

Although atypical antipsychotic medications are now widely used to treat delusions, aggression and agitation in people with Alzheimer disease and other dementias, concerns have arisen about the increased risk for cerebrovascular adverse events, rapid cognitive decline, and mortality with their use.

This meta analysis concluded that death occurred more often among patients randomized to drugs (118 [3.5%] vs. 40 [2.3%]). Sensitivity analyses did not show evidence for differential risks for individual drugs, severity, sample selection, or diagnosis. Atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives.

1. Shneider LS, Dagerman KS, Insel P. Risk of Death with Atypical Antipsychotic Drug Treatment for Dementia. JAMA 2005;294:1934-43.

Creating Animal Models for the Study of Psoriasis

Psoriasis is a chronic inflammatory disease of unsolved pathogenesis affecting skin and joints in 1-3% of the general population. The skin lesions show hyperproliferation and altered differentiation of epidermal keratinocytes, marked infiltrates of T cells and neutrophils, and a distinct increase of skin capillaries. Although at least six different psoriasis susceptibility loci, designated PSORS1-PSORS6, have been mapped by using genome-wide scans, the cause of psoriasis remains unknown.

Research into the pathogenesis of psoriasis has been hampered by the lack of an animal disease resembling this common human skin disorder. Previous attempts to faithfully reproduce the psoriatic phenotype through expression of inflammatory mediators or keratinocyte growth factors gave

rise to phenotypes with only partial resemblance to psoriasis. Moreover, most mouse models showed no arthritic lesions, although these are present in up to 40% of patients with psoriasis. This represents one of the most significant hurdles in the study of psoriasis.

The present report published in Nature[1] lays the foundation for crucial pre-clinical work in this area, by developing a suitable mouse model for adult human psoriasis. The authors first show that that in psoriatic lesions, epidermal keratinocytes have decreased expression of JunB (a gene localized in the psoriasis susceptibility region PSORS6). They then induce epidermal deletion of JunB and its functional companion c-Jun in adult mice, leading to a phenotype resembling the histological and molecular hallmarks of psoriasis, including arthritic lesions. The development of this phenotype in adult mice takes about two weeks.

The detailed description of the development of psoriasis in the mouse model can be summarized by the following:

(i) The abrogation of JunB/activator protein 1 (AP-1) in keratinocytes triggers chemokine/cytokine expression

(ii) This recruits neutrophils and macrophages to the epidermis

(iii) Thereby contributing to the phenotypic changes observed in psoriasis.

The authors believe that these data support the hypothesis that epidermal alterations are sufficient to initiate both skin lesions and arthritis in psoriasis. This model is also important because of the inducible, high-efficiency and rapid development of the phenotype, which provides a basis for the study of this serious disease.

1. Zenz R, Eferl R, Kenner L. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. NATURE 2005;437:369-75.

Screening for Breast Cancer

Two profound studies in NEJM published in October 2005 add sound evidence to the already abundant data on the role of breast cancer screening in saving lives.

The first study by Berry et al.[1] uses modeling techniques to assess the relative and absolute contributions of screening mammography and adjuvant treatment to the reduction in breast-cancer mortality in the United States from 1975 to 2000. Seven independent statistical models of breast-cancer incidence and mortality were developed by various investigators, all of whom used the same sources to obtain data on the use of screening mammography, adjuvant treatment, and benefits of treatment with respect to the rate of death from breast cancer. The proportion of the total reduction in the rate of death from breast cancer attributed to screening varied in the seven models from 28 to 65% (median, 46%), with adjuvant treatment contributing the rest. All seven statistical models showed that both screening mammography and treatment have helped reduce the rate of death from breast cancer in the United States significantly. This report is also a reminder that the technical aspects of mammography influence the quality of breast cancer screening.[3]

The report by Pisano et al.[2] of the results of the Digital Mammographic Imaging Screening Trial (DMIST) adds important information that physicians will use to assess the value of a new technique in mammographic screening: digital-image acquisition and storage.

Film mammography has limited sensitivity for the detection of breast cancer in women with radiographically dense breasts. Thus the authors assessed whether the use of digital mammography would avoid some of these limitations.

A total of about 50 thousand asymptomatic women presenting for screening mammography at 33 sites in the United States and Canada underwent both digital and film mammography. In the entire population, the diagnostic accuracy of digital and film mammography was similar. However, the accuracy of digital mammography was significantly higher than that of film mammography among women under the age of 50 years (difference in the area under the curve, 0.15; 95% confidence interval, 0.05 to 0.25; P=0.002), women with heterogeneously dense or extremely dense breasts on mammography (difference, 0.11; 95% confidence interval, 0.04 to 0.18; P=0.003), and premenopausal or perimenopausal women (difference, 0.15; 95% confidence interval, 0.05 to 0.24; P=0.002). The authors conclude that the overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer is similar, but digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women. Thus, the recommendation is that in facilities in which digital mammography is available, it is appropriate for women in subgroups in which this approach has a demonstrated advantage over film mammography. However, in the bulk of the screening population, either technique is acceptable, and film mammography may confer a nonsignificant advantage.[3]

The message is simply that any good quality screening saves lives.

1. Berry DA, Cronin KA, Plevritis SK. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-92.

2. Pisano ED, Gatsonis C, Hendrick E. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005;353:1773-83.

3. Dershaw D. Film or Digital Mammographic Screening? N Engl J Med 2005;353:1846-7.