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Editorial

Ultrasound and ovarian cancer

Asim Kurjak

It is now 30 years since Ian Donald published the first paper on the use of ultrasound in obstetrics and gynecology. Since then, this technology has revolutionized the management of obstetrics. Transvaginal ultrasound has the potential to make a major impact in gynecology and obstetrics and with color flow imaging is the most exciting recent development in the use of ultrasound in this speciality.

Transvaginal sonography, color flow imaging and Doppler enable the investigator to study the female genital system in more detail than was previously possible. This technology provides greater resolution and better Doppler signals than transabdominal ultrasound and can map the course of blood vessels in the pelvis. With a vaginal probe combining these modalities, structural and dynamic studies can be performed simultaneously, offering new insight into blood flow in the pelvis. Information is rapidly accumulating from such studies on the physiology and pathology of the female pelvis, and initial results suggest that this technique may discriminate between benign tumors and invasive cancers of the ovary. This raises the possibility of applying these advances in ultrasound to detect early localized cancer of the ovary.

Ovarian cancer kills more women than cancer of the corpus uteri and cervix combined. The American Cancer Society estimates that approximately 20 000 new cases were diagnosed in The United States of America in 1989 and that close to 60% of those affected died of the disease. The incidence is currently rising and, despite advances in surgery and chemotherapy, the prognosis has remained unchanged for 30 years. Symptoms may mimic gastrointestinal and urinary disorders and do not develop until metastases occur. Thus, more than 60% of patients present with late stage disease. The 5-year survival rates for stages III and IV are 13% and 4%, respectively.

Progress has been made towards a better understanding of some of the features of this insidious disease. At the recent 3rd Biennial International Forum on Ovarian Cancer (Helene Harris Memorial Trust, Charleston, USA, 17–20th April, 1991) Dr Bruce Ponder presented data on patients with a family history of ovarian cancer: women who have one relative with ovarian cancer have a threefold increase in their own risk of developing the disease by 70 years of age. Those with two affected close relatives may have a risk as high as 30%. Such patients should be offered the best screening procedure currently available. As the efficacy of such programs is as yet unproven, prophylactic oophorectomy should be considered once child-bearing is complete. These data strongly support the theory that a proportion

of ovarian cancers are familial and pose the challenge of identifying the gene or genes that predispose to the development of this malignancy in women in these families. The characteristics and function of the genes will shed light on the pathogenesis of ovarian cancer in general. A limiting factor in genetic studies will be the availability of well-documented families. Clinicians are urged to take a family history from all their patients and to inform the relevant study group when cases of familial ovarian cancer are identified. National and international cooperation will also be essential.

Learning about angiogenesis has also broadened our understanding of carcinogenesis. Since Folkman's first observation in 1971, it has been established that unrestricted growth of a cancer is dependent upon this process. It is a physiological phenomenon in the endometrium at implantation, in the ovary at ovulation and formation of the corpus luteum, and during embryonic development. It only occurs at other sites of the adult body as part of a pathological process, such as wound healing or oncogenesis. Many conditions of unknown etiology or pathogenesis are associated with angiogenesis. Neovascularization is associated with retrolental fibroplasia and diabetic retinopathy, two conditions which may lead to blindness. New capillaries invade the joints in arthritis. Solid tumors also induce angiogenesis

but it differs temporally from the other types described. In physiological conditions, such as the development of the corpus luteum, it is present for a limited period of time only and then subsides. In contrast, cancer-induced angiogenesis is not self-limiting and continues until the host dies or the tumor is eradicated.

Color Doppler can detect the small low-resistance vessels which develop in neoplastic tissue. This allows accurate placement of the pulsed Doppler range gate and waveform analysis. Pourcelot's resistance index or pulsatility index may be used to quantify the information obtained. In the past, it was only possible to discover asymptomatic cancer in an ovary 3.5–6.0 cm in diameter as a chance finding at laparotomy. Detecting ovarian cancer at an early stage was unusual due to the lack of symptoms. With color Doppler ultrasound, it is now possible to diagnose ovarian cancer non-invasively because of the characteristic patterns of flow in the newly formed vessels in the tumor. Furthermore, data from the Zagreb and London groups show that it is realistic to expect to do so at as early a stage as Ia.

A total of 10 000 women will develop ovarian cancer within the next 12 months in Western Europe. In a population-based screening program for ovarian cancer using transabdominal ultrasound, Campbell and colleagues screened approximately 5000 women at roughly 18-month intervals. They detected four stage Ia and one stage Ib primary ovarian cancers. The main criticism of the technique used was that it was unable to discriminate between benign and malignant lesions and as a result many unnecessary operations were performed.

The Zagreb group has now studied over 14 000 asymptomatic or minimally symptomatic women screened for ovarian cancer using transvaginal color Doppler ultrasound. The resistance index (RI) was calculated as the mean from five cardiac cycles. Altogether 624 benign adnexal masses were detected and all but one had an RI greater than 0.40. There were 47 primary ovarian cancers. Neovascularization and an RI of 0.40 or less were found in six of the seven stage I and 39 of the 40 late stage (III and IV) tumors. It was also detected in all the secondary (9) ovarian cancers. Any diagnostic program involving new technology is likely to have false-positive and false-negative results. In this study, there was one false-positive and two false-negative observations. The sensitivity of the test was 96.4%, specificity 99.8% and positive predictive value 98.2%. The finding of seven stage Ia cancers is encouraging, as treatment at this early stage should be excellent if one extrapolates from results of treating patients who present clinically. The group emphasized the importance of thorough examination of ovaries with color Doppler regardless of their size and B-mode ultrasound appearance.

The ideal screening test for ovarian cancer should detect the disease in a premalignant phase and hence provide a method for prevention of invasion. Unfortunately, as yet, a well-defined precancerous lesion of the ovary, analogous to cervical intraepithelial neoplasia or atypical endometrial hyperplasia, has not been found. Indeed, the identification of such a stage might reduce the number of deaths further still and the search must continue.

Transvaginal sonography has been combined with the measurement of tumor-associated antigens in the serum to screen for ovarian cancer. The most thoroughly investigated to date is CA-125. When used alone, it demonstrates inadequate sensitivity to be used as a screening test for ovarian cancer. Jacobs and colleagues attained a specificity of 99.9% when CA-125 and ultrasound were used in combination, but numbers were small and only one cancer was detected. The sensitivity of this multimodal approach was not mentioned. The use of complementary markers may improve sensitivity but a suitable combination has not yet been assessed. The conviction that such synergism will evolve is stressed and available banked serum should be tested with this aim in mind. Such research is currently being conducted in centers throughout the world.

Population screening with ultrasound has an apparent high sensitivity but poor specificity. To reduce the false-positive rate in such a program, color Doppler and morphological scoring systems have been used. Although initial results are exciting, it must be remembered that as yet criteria do not exist to discriminate between a corpus luteum, a corpus luteum cyst, an ectopic pregnancy and malignant transformation. To a certain extent, these limitations apply to the premenopausal population and, at present, transvaginal color Doppler is the best available method for screening the postmenopausal population. The median age for stage I ovarian cancer is 54 years. For stages II and III, it is 58 and 62 years, respectively. The group aged 60–74 years is most likely to have advanced stage disease. The likelihood of offering effective treatment to this group is minimal. In the future, postmenopausal women will constitute a larger proportion of the patient population. This has important implications for screening. The predominant issues of the past relating to obstetrics, family planning and contraception will be replaced by those of the future, such as preventive medicine and caring for the elderly. The present generation of gynecologists must decide how to provide appropriate care for these women. They will undoubtedly aim to detect ovarian cancer early.

On the basis of available evidence, the time is ripe for a randomized controlled trial to assess whether screening for ovarian cancer can reduce mortality in the general population. If such a trial is not instituted soon, screening will be incorporated into clinical practice and the opportunity to assess it scientifically will be lost forever. Ultrasound has better screening parameters than other modalities at the present time and is, therefore, more likely to produce successful results. It is our belief that the detection of abnormal tumor angiogenesis by transvaginal color Doppler holds great promise as a method of screening for ovarian cancer.

It is hoped that screening for ovarian cancer with transvaginal color Doppler will prove as efficacious as screening for cervical cancer with the Pap smear. As the incidence of ovarian cancer is higher than that of cervical

cancer, an effective screening program for the former is indicated from a practical and a medical point of view.

In aiming for the early diagnosis of ovarian cancer, we have identified and labelled tumor angiogenesis. However, to observe and recognize is not to understand. We understand little of this process and have much to learn. However, to quote Winston Churchill, 'This is not the beginning of the end, but only the end of the beginning'.

Opinion

First-trimester fetal karyotyping: CVS or early amniocentesis?

Despite the widespread introduction of second-trimester amniocentesis in the early 1970s, the birth prevalence of Down's syndrome and other major chromosomal disorders has not fallen significantly over the past 15 years. The two principal reasons are that, firstly, the majority (70–80%) of affected babies are born to mothers under 35 years of age and, secondly, the uptake of second-trimester amniocentesis is low, which may in part reflect the reluctance of patients to have a late diagnosis and thus a possibility of second-trimester termination.

The majority of procedures for fetal karyotyping are performed for low-risk indications, such as advanced maternal age, maternal anxiety or a previous child with a mutant chromosomal abnormality. Indeed, screening policies advocate counselling in favor of prenatal diagnosis to women with risks as low as 1 in 280. The logic behind this policy is to provide testing when the risk from the procedure balances the risk of the disorder.

The Canadian trial and recently the MRC European trial showed that a woman allocated to first-trimester chorionic villus sampling (CVS) has an 1.7–4.6% less chance of a successful pregnancy outcome than a woman allocated to second-trimester amniocentesis[1,2]. Furthermore, recent reports of facial and limb abnormalities occurring in cases where CVS was performed before 10 weeks' gestation, although small in number, have caused such concern that CVS at these gestations is likely to be abandoned. Nevertheless, although CVS is shown to be potentially less safe and more prone to diagnostic error, a first-trimester procedure is infinitely preferable to testing in later pregnancy, because it provides early reassurance from normal results for the majority of parents and in those unfortunate few with an affected fetus, the mother can have a safer and emotionally less traumatic first- rather than second-trimester termination.

The new non-invasive screening methods using maternal serum triple biochemistry and ultrasonography can potentially detect more than 70% of the chromosomally abnormal fetuses. Thus, since at present these tests can only be done in the second trimester of pregnancy, first–trimester karytyping may become obsolete. However, since there is strong preference by patients for early prenatal diagnosis, it is more likely that the new methods of screening will be widely adopted only when they can be applied in the first trimester. In this respect, there is still a major need for improvement in early invasive techniques.

As a result of the Canadian, the MRC European and the Danish trials, we now have information about the comparative risks of first-trimester CVS and second-trimester amniocentesis but not about the safety and diagnostic accuracy of the tests when they are done at comparable gestational ages[1,3]. The preliminary report on the prospective randomized trial of Byrne and colleagues has demonstrated that early amniocentesis and CVS at 10–13 weeks' gestation have similar success rates in obtaining samples which allow successful cytogenetic analysis. However, the safety and diagnostic accuracy of early amniocentesis cannot be assumed to be the same as that for second-trimester amniocentesis. For example, at earlier gestations the volume of fluid removed constitutes a much greater proportion of the total, which may affect fetal loss and fetal lung function. Therefore, as suggested by Byrne and colleagues, early amniocentesis should not be introduced into clinical practice before the problems of safety and accuracy have been carefully evaluated by large prospective randomized trials.

C. M. GOSDEN

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