Obstetrics and Gynaecology

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A review of publications relating to significant advances in the specialty of Obstetrics and Gynaecology over the past four years will be discussed: topics reviewed will have an important impact on reducing maternal/fetal morbidity and mortality and should improve on woman's health care.

Prevention of Preterm Delivery

Preterm labour is the most common cause of fetal morbidity and perinatal mortality. Women who have had a spontaneous preterm delivery will be at an increased risk of having a preterm delivery in subsequent pregnancies and among the complications related to prematurity, there are respiratory distress syndrome, necrotising enterocolitis and intraventricular haemorrhage.

Progesterone applied as a weekly intramuscular injection or as daily vaginal pessaries, was utilised in two double-blind, placebo-controlled trials involving pregnant women with a documented history of spontaneous preterm delivery. In one study, treatment with 17 alpha-hydroxyprogesterone caproate (17P)[1] intramuscularly on a weekly basis, was initiated at 16 to 20 weeks of gestation and continued till 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation.

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Treatment with 17P significantly reduced the risk of delivery at less than 35 weeks of gestation (incidence, 20.6 % vs. 30.7 %; RR, 0.67, 95 % CI, 0.48 to 0.93), and delivery at less than 32 weeks of gestation (11.4 % vs. 19.6 %; RR, 0.58, 95 % CI, 0.37 to 0.91. There were also significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage and need for supplemental oxygen in the progesterone treated group.

In another study utilising daily progesterone pessaries (100mg), between 24 and 34 weeks gestation preterm delivery was noted in 2.8% in the progesterone group (72 patients) and 18.6% in the placebo group (74 patients) giving a reduction of 85%.[2] Both studies show great promise in the application of progesterone as a safe prevention against preterm labour.

Treatment of Menorrhagia

Twenty years ago, hysterectomy was the mainstay of treatment for menorrhagia, with over 60% of patients referred for this symptom being treated with this surgical procedure. The levonorgestrel intrauterine system (LNG-IUS, Mirena) has been shown to be highly effective in reducing menstrual blood loss by up to 80% and consequently a significant reduction in the numbers of patients proceeding to hysterectomy has been noted.

Over the years 1989-1990 till 2002-2003, NHS hospital episode statistics were examined for hysterectomy rates, compiled from data submitted by over 300 NHS trusts in the U.K.[3] From 1989-1990 to 1994-1995 an average of 23,056 hysterectomies a year were performed for menorrhagia in the U.K. In 2002-2003, 8,332 hysterectomies and 4,921 endometrial ablations were performed, representing a reduction of 64% in the number of hysterectomies and a reduction of 43% (13 253 *v* 23 284) in the total number of operations for menorrhagia compared with 1989-90. Medical treatments for menorrhagia are increasingly being applied with success reducing the need to resort to surgical intervention.

Early Diagnosis and New Chemotherapy Regimen for Women with Ovarian Cancer

Approximately 25,000 new cases of ovarian cancer are diagnosed in the United States each year. This disease is often diagnosed at a late stage when the disease has led to ascites and abdominal metastasis and the mortality within five years of diagnosis is 70%.

Early detection of ovarian cancer is urgently needed in view of the lethal nature of this disease. The rationale behind a study

on proteomic spectra relies on the fact that pathological changes within an organ might be reflected in proteomic patterns in serum, as detected by mass spectrometry. A bioinformatics tool was developed to identify proteomic patterns in serum that distinguish neoplastic from non-neoplastic disease within the ovary. A pilot study of proteomic spectra derived from analysis of serum from 50 controls and 50 patients with ovarian cancer were analysed and a proteomic pattern that completely discriminated cancer from non-cancer was discovered. The same pattern was applied to an independent group of 116 blinded serum samples: 50 from women with ovarian cancer, and 66 from controls. The proteomic spectral pattern correctly identified all 50 ovarian cancer cases in the blinded group, including all 18 stage I cases. Of the 66 cases of non-malignant disease, 63 were recognised as not cancer. This result yielded a sensitivity of 100% (95% CI 0.93 to 1.00), specificity of 95% (0.87 to 0.99), and positive predictive value of 94% (0.84 to 0.99). A large prospective population-based study is underway of proteomic pattern technology as a screening tool for all stages of ovarian cancer in high-risk and general populations.[4]

Ovarian cancer Treatment

Chemotherapy with carboplatin, a platinum-based drug, and a taxane-based drug (paclitaxel) is considered to be the standard care for the initial treatment of ovarian cancer. However more than a third of patients given standard treatment suffer from severe peripheral neuropathy. A new taxane-based chemotherapy using docetaxel with elevated anti-tumor activity on ovarian cancer and a favourable side-effect profile has been administered in a new trial. In this recent phase III trial, the combination of docetaxel and carboplatin chemotherapy was compared with the standard treatment of pactlitaxel and carboplatin as first-line treatment for women diagnosed with stage Ic-IV epithelial ovarian or primary peritoneal cancer. The overall survival rates at two years were similar to standard therapy but the nerve fibre toxicity was lower in the docetaxel-carboplatin group (11% versus 30%).[5]

Safety and Usefulness of Ultrasound in Obstetrics

Since 1990, an Australian group randomised 3000 pregnancies to a single mid-trimester ultrasound or a series of five ultrasounds, to see if routine or serial ultrasonographic investigations made a difference in perinatal or long-term outcome. This group has published their findings of children who are now eight years of age. This is the fifth assessment of these children since birth, and the parameters measured included speech, language, behaviour and neurological development. Both groups of children had similar scores for the parameters measured and were doing equally well at junior school level.[6] This longitudinal study confirms the long-term safety of serial obstetric ultrasound which is frequently being applied as a form of screening and monitoring tool.

The usefulness of serial growth and Doppler ultrasound assessments has been shown in several articles as the following paper demonstrates. Longitudinal changes in the middle cerebral artery blood flow in severely growth restricted fetuses were serially examined by Doppler. Outcome measures included indication for delivery, umbilical venous pH and admission to and length of stay in neonatal intensive care.

The middle cerebral artery pulsatility index showed rapid and sharp changes between examinations in those severely growth restricted fetuses which required delivery before 34 weeks. The middle cerebral artery pulsatility index demonstrated greater variation in those fetuses with cord pHs of less than 7.25. The length of stay in neonatal intensive care decreased with increasing gestational age and birth weight.[7]

Menopause

The Woman's Health Initiative (WHI) Study

The Woman's Health Initiative (WHI) was a prospective placebo/controlled study of sex hormones used as replacement therapy in women during menopause. It was designed to study whether placing a postmenopausal woman on HRT is beneficial to their long and short term cardiovascular health, bearing in mind that cardiovascular disease is the most common cause of death in post-menopausal women.

The mean age of women on entering the study was 63 years (on average 15 years post-menopausal). The dose of oestrogen and progesterone given to the average 63-68 year old woman in the study was the same as that usually given to their 40-50 year old counterparts in the trial and roughly twice the physiological dose for the older-age group woman.

Oestrogens have a beneficial effect on the lipid profile, but this may be opposed by the progestins component in HRT. Amongst the progestins with such a deleterious effect is medroxyprogesterone acetate (MPA) which was used in the WHI study.

The progestin used and the age of the women recruited may in part explain the results obtained. Estimated hazard ratios (95% confidence intervals [CIs]) were as follows: coronary heart disease, 1.29 (1.02-1.63); breast cancer, 1.26 (1.00-1.29); stroke, 1.41 (1.07-1.85); PE, 2.13 (1.39-3.25); colorectal cancer, 0.63 (0.43-0.92); endometrial cancer, 0.83 (0.47-1.47); hip fracture, 0.66 (0.45-0.98).[8] The deleterious effect of the progestin used became more apparent by its absence in the estrogen only arm of the WHI study. Estimated hazard ratios (95% CI) were: coronary heart disease 0.91 (0.75-1.12); breast cancer, 0.77 (0.59-1.01); stroke, 1.39 (1.10-1.77); PE, 1.34 (0.87-2.06); colorectal cancer, 1.08 (0.75-1.55); and hip fracture, 0.61 (0.41-0.91).[9]

The WHI study was a study of HRT on relatively old post menopausal women, a large proportion of whom were overweight, had cardiac risk factors and/or a family history of breast cancer. Post/perimenopausal women normally requiring HRT are at least 10-15 years younger than the women recruited in the WHI study.[10]

Million Woman Study

The Million Woman Study was carried out over five years up to early 2001. NHS breast screening centres participating included a study questionnaire with a letter of invitation "to assess the risk for breast cancer" sent two to six weeks before mammography. The questionnaire contained questions on various factors, including use of HRT (what, when, for how long) and menstrual history. There were 1,084,100 women in the study and at recruitment the average age was 56 years. Past use, even for less than a year, was associated with no increased risk. Over 4.1 years of HRT use there was one extra breast cancer death for every 16,000 women currently using HRT. Five extra cases of breast cancer were identified among users of oestrogen-only HRT and 19 among users of oestrogen-progestagen combinations for every thousand postmenopausal women who begin 10 years of HRT use at age 50.[11]

The million women study has however received severe criticism regarding the basic methodology utilised to implement the study especially in view of strong biases in recruitment.

Nurses Health Study

The Nurses Health Study followed over 100,000 women for 24 years and was set up to examine a number of parameters including the relationship between exercise, body mass index (BMI) and risk of death. In this study, the effects of obesity were related to the risk of death, which risk increased, regardless of the level of physical activity. Although higher levels of physical activity appeared to be beneficial at all levels of adiposity, it did not eliminate the higher risk of death associated with it. Even modest weight gain during adulthood, independent of physical activity, was associated with a higher risk of death.

Conclusions from the study show that, 31 percent of all premature deaths, 59 percent of deaths from cardiovascular disease, and 21 percent of deaths from cancer among nonsmoking women, could be accounted for from the excessive weight (defined as a body-mass index of 25 or higher) and physical inactivity (less than 3.5 hours of exercise per week). Both increased adiposity and reduced physical activity are strong and independent predictors of death.[12]

From the Nurses Study, evidence suggested that impaired intrauterine fetal growth is associated with cardiovascular disease later on in life. Risk factors for cardiovascular disease such as diabetes and hypertension showed an increased prevalence later on in adult life, in individuals who had a fetal history of growth restriction.[12]

Venous Thromboembolism in Pregnancy

Venous thromboembolism (VTE) is a common cause of maternal morbidity and mortality. It can be reduced by either prophylaxis and/or treatment in women at increased risk or by extensively investigating women who present with symptoms that raise a suspicion of clinical VTE. Venous thromboembolism is commoner in pregnant women suffering from thrombophilia. Besides VTE, pregnancy complications such as placental infarction, including miscarriage, intrauterine growth retardation, preeclampsia, abruption, and intrauterine death may arise.

Often in combination with aspirin, anticoagulant therapy is administered for the prevention of pregnancy loss in women with anitiphospholipid (APLAs) syndrome or thrombophilia and previous pregnancy losses. Patients with APLAs and no prior VTE or pregnancy loss should be considered to have an increased risk for the development of venous thrombosis and pregnancy loss. One of the four approaches that can be implemented include mini-dose heparin, prophylactic low molecular weight heparin (LMWH), or low-dose aspirin, 80 to 325 mg daily. The indication for active prophylaxis is stronger in antithrombin III -deficient women than the other thrombophilias.

For multiple (more than two) episodes of VTE, and/or women receiving long-term anticoagulation therapy (eg, single episode of VTE, either idiopathic or associated with thrombophilia), adjusted-dose unfractionated heparin or either prophylactic or adjusted-dose LMWH, followed by resumption of long-term anticoagulation therapy postpartum is indicated.[14]

Postmenopausal Osteoporosis

The American College of Obstetricians and Gynaecologists has recognized that postmenopausal osteoporosis is the epidemic of the future. It has published clear guidelines as to the role of gynaecologists in the prevention and therapy of this condition.[15]

A bone density measurement one standard deviation below normal increases the risk that a post-menopausal woman will sustain a fracture by 50%. Other features associated with fracture risk are age, female sex, small body frame, and white race. The National Osteoporosis Risk assessment study however indicated that 50% of postmenopausal women who sustained a fracture were osteopaenic rather than osteoporotic suggesting that nondensity variables may be also relevant.[16] As regards vertebral fractures which affect 25-40% of the postmenopausal population a possible nondensity variable may be the shock-absorbing intervertebral discs.[17]

It has been shown that HRT will help to preserve the bone mass. The WHI study showed this even in those women who started HRT well after the menopause. As primary prevention, it lowers hip fracture rates by about a third (RR 0.67).[8] Selective oestrogen receptor modulators (SERM) which will reduce bone resorption as well as reducing the risk of breast cancer are being investigated. At present raloxifene is the only SERM registered for osteoporosis prevention. Vitamin D (800iu daily) supplementation and an intake of 800-1200mg of calcium daily is related to a significant reduction in fracture rate in the elderly.

Prolapse and Stress Incontinence

As postmenopausal women continue to outlive men they

tend to become a greater proportion of all medical health consumers and their health, both in terms of prevention and in treatment will be the focus of future research.

Millions of women have genital prolapse, with or without stress incontinence, and this greatly influences their quality of life. A recent study reviewed asymptomatic women and assessed prolapse/descent as measured from the hymen or below. Subjects underwent a Pelvic Organ Prolapse Quantification examination during a maximal Valsalva maneouvre and in addition completed a questionnaire.

Hormone therapy was not associated with prolapse (P =0.9). On multivariable analysis, less education (odds ratio [OR] 2.16, 95% CI 1.10-4.24) and higher vaginal parity (OR 1.61, 95% CI 1.03-2.50) were associated with prolapse at the level of the hymen. For prolapse defined by the leading edge at or below the hymen, older age had a decreased risk (OR 0.50, 95% CI 0.27-0.92) and less education, and larger babies had an increased risk (OR 2.38, 95% CI 1.31-4.32 and OR 1.97, 95% CI 1.07-3.64, respectively). Some degree of prolapse is found in over 25% in older women of 70 years of age. Minor degrees of uterine and vaginal wall prolapse is so common as to be regarded as normal in the elderly.[18]

At present the most successful surgical intervention for stress incontinence is the tension free tape (TVT). A cure rate from stress incontinence of over 85 % has been quoted in various prospective studies.

Another recent advance in the medical treatment of urinary stress incontinence is duloxetine, targeting increased urethral tone in response to raised intra-abdominal pressure. It is a balanced serotonin re-uptake inhibitor which has been found to be helpful in mild to moderate stress incontinence. In a study utilising duloxetine, severe sufferers were noted to have urethral hypermobility plus intrinsic sphincter deficiency with scarring, fibrosis or fixity. Duloxetine efficacy was demonstrated even in women with or without sphincter deficiency and women noted improvement within two weeks of starting treatment: this was maintained for the whole eight weeks of the trial period. Side effects were common but these were usually transient and subsided with time. Quality of life was improved to such an extent that 20% of women initially booked for surgery were reconsidering their choice of treatment.[19]

Human Papilloma Virus (HPV) and cervical cancer

A conservative estimate indicates that worldwide, a quarter of a million women die each year from cervical cancer and where resources are scarce, and cytological screening is not readily available, this carcinoma is still common.

The causal role of HPV types 16 and 18 has been clearly established, with highly sensitive PCR techniques demonstrating HPV DNA in 100% of histologically confirmed cervical cancers. Persistent infection is the chronic complication, especially with types 16 and 18, and monovalent vaccine testing appears effective.

A cohort of women was followed for around 17.4 months after completing the vaccination regimen. The incidence of persistent HPV-16 infection was 3.8 per 100 woman-years at risk in the placebo group and 0 per 100 woman-years at risk in the vaccine group (100 % efficacy; 95 % CI, 90 to 100; P<0.001). All nine cases of HPV-16–related cervical intraepithelial neoplasia occurred among the placebo recipients. Administration of this HPV-16 vaccine appears to reduce the incidence of both HPV-16 infection and HPV-16–related cervical intraepithelial neoplasia.[20]

The extensive bivalent trials by Harper *et al* look even more interesting.[21] Women were vaccinated against the most common oncogenic human papillomavirus (HPV) types, HPV-16 and HPV-18. A randomised, double-blind, controlled trial was designed to assess the efficacy, safety, and immunogenicity of a bivalent HPV-16/18 L1 virus-like particle vaccine for the prevention of incident and persistent infection with these two virus types, associated with cervical cytological abnormalities, and precancerous lesions. The study involved 1113 women aged between 15-25 years of age, randomised to receive three doses of the vaccine formulated. In the according-to-protocol analyses, vaccine efficacy was 91.6% (95% CI 64.5-98.0) against incident infection and 100% against persistent infection (47.0-100) with HPV-16/18. In the intention-to-treat analyses, vaccine efficacy was 95.1% (63.5-99.3) against persistent cervical infection with HPV-16/18 and 92.9% (70.0-98.3) against cytological abnormalities associated with HPV-16/18 infection. The vaccine was generally safe, well tolerated, and highly immunogenic. The bivalent HPV vaccine was efficacious in prevention of incident and persistent cervical infections with HPV-16 and HPV-18, and associated cytological abnormalities and lesions. It has been postulated that vaccination against HPV-16 and HPV-18 could substantially reduce incidence of cervical cancer by up to 70%.

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