Practice And Research Beyond Boundaries

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Summary

The UK white paper on 'Saving Lives Our Healthier Nation' calls for reducing premature deaths from cardiovascular diseases and cancer. In this review we discuss how obstetricians and gynaecologists by taking a proactive approach in practising medicine on available evidence can contribute to reduction in cardiovascular diseases. Research in molecular genetics has led to emergence of possible new technologies for screening and early detection of gynaecological cancers. Surgical options to improve blood supply to the diseased myocardium may not be always effective. Transplantation of foetal cardiomyocytes and its subsequent neovascularisation may be feasible in the future as initial animal experiments show promising results.

Introduction

Heart disease is the commonest cause of death in most developed countries and is increasing in poor countries. The UK government launched the White paper "Saving Lives": Our Healthier Nation on 6th July 1999, setting out health strategy for England. The strategy focuses on four priority areas: Coronary Heart disease and Stroke, Accidents, Cancer and Mental illness, the principal causes of premature death and avoidable ill health in this country.

Obstetrics and Gynaecology is an unique speciality. It can lay claim on the entire female sex as its potential patients. This virtually mean the half of human race. Considering the fact that millions of women around the world are disadvantaged in obtaining health care the implications for practising this speciality are immense. As obstetrician and gynaecologists we are good in practicing medicine within boundaries of the hospital. Even with our practice within the hospital we can take a pro-active approach in practising medicine based on available evidence to reduce mortality and morbidity due to the killer diseases that are the National Priority. Our practice and research can be focused on what affects the majority and how we can contribute to 'Our Healthier Nation'. In this paper we discuss about how obstetricians and gynaecologists can contribute to reduction of Coronary Heart Disease.

Women in the Reproductive age group

Mortality rates per million female population aged 15-44 years based on ICD codes (9th revision) in England & Wales for the year 1992 were as follows:

Road Deaths 80	Pregnancy related complications 60.
Ovarian Cancer 48	Home Accidents 40
Myocardial infarction 39	Venous Thromboembolism 11
Cerebral infarct 8	Pulmonary embolism 3

These statistics give us some food for thought.

Oral Contraceptive use and cardiovascular disease

Although most women cite breast and reproductive cancers as the diseases they most fear, in fact

cardiovascular disease is much more likely to kill them. 500,000 American women die each year of diseases of the heart and blood vessels compared with 189,000 who die of all cancers combined.(Legato 1996). However the incidence of myocardial infarction and stroke not associated with pregnancy is rare until age 35, (Petitti et al 1997) but rises after 35 due to increased incidence of arterial diseases. The use of oral contraceptive and the risk of cardiovascular disease has always been a matter of debate. Oral contraceptives have been studied more intensively than any other medication in the history yet it has generated more heat than light in the media with series of 'pill scares'. The shift to third generation pills in the early 1990s was largely based on the claims of superior cardiovascular safety and indeed the Transitional study (Lewis et al. 1996) suggested possible reduced risk of myocardial infarction. In the largest study, the MICA (Nicholas et al 1999) study from the United Kingdom, no difference in risk of myocardial infarction was found between second and third generation contraceptives. More importantly there is no increased risk of myocardial infarction in users of oral contraceptives. The risk is usually confined to women with known cardiovascular risk factors and women who wish to preserve their cardiovascular health should stop smoking, above all else. More contentious has been the effect of third generation contraceptives on venous thromboembolism. The incidence of venous thromboembolism in healthy, non pregnant women not taking a combined oral contraceptive is about 5 cases per 100,000 whereas 60 cases per 100,000 pregnancies. (Committee of safety of Medicine 1999). The risk of thrombo-embolism increases with pill usage. Committee of safety of medicine quotes a figure of 15 per 100,000 for second generation pill and 25 cases per 100,000 for the third generation pills. The proactive use of the oral contraceptive pill reduces the risk of venous thrombo-embolism by 12 times by preventing pregnancy with high degree of effectiveness. Indeed the above figures are also reassuring in terms of cardiovascular health and prescribing the combined pill.

Twenty five years follow up of cohort of 46,000 UK women from RCGP oral contraception study found a decrease in mortality from ovarian cancer. The effect persisted 10 years after the study. (Beral et al 1999). The same study found an increased incidences of death from cervical cancer among women using oral contraceptives but this reflect sexual behaviour than pill per se.

Polycystic ovary and Myocardial Infarction

Those women in the reproductive age group with polycystic ovaries and show signs of obesity, hyperinsulinaemia, hypertension and hyperlipidaemia have seven times higher risk of myocardial infarction (Kidson 1998). These women will benefit by active treatment using oral contraceptive with non androgenic progesterone.

Proactive use of the pill will go a long way to prevent the grief of unplanned pregnancy, hazards of septic abortion and more importantly maternal deaths. In places such as parts of rural Africa, where women may have 1 in 15 lifetime risk of dying from pregnancy related causes the effectiveness of oral contraceptives in preventing pregnancy will be overwhelmingly important. Spacing pregnancy can also be expected to reduce mortality in such populations.

Alcohol consumption, Smoking and Cardiovascular mortality.

Eat,drink and be merry, for tomorow we die, has always carried with its assumption that all three activities directly contribute to undesired outcome. That's what 'the doctor ordered–more alcohol and sex'. (Cleare et al 1997). Undoubtedly like smoking, heavy drinking increases the risk of death from various causes. However there is now convincing evidence that one can reduce one's risk of heart disease by drinking moderate amount each day in middle and old age. (Doll 1997). There is at least one third reduction in mortality in vascular disease with consumption of small to moderate amount of alcohol usually between one to four units. The benefit of taking alcohol for women has not been convincing. This may be due to the cardioprotective effect already offered by the oestrogenic state in the females. The beneficial effect is due to the content of ethanol, not to the characteristics of

any particular type of drink. Low lipoprotein concentration induced by ethanol may be one factor explaning low mortality due to coronary artery disease in social drinkers.

Smoking

Cigarette smoking is an establised risk factor for cardiovascular disease. The risk of coronary artery disease in men is directly proportional to the number of cigarettes smoked. This relationship is less certain, but still important in women. Other variables like concurrent use of contraceptive pills, genetic predisposition may even increase the risk of coronary artery disease. It is said that risk of smoking actually declines to almost normal after 10 years of abstention. We should be proactive in developing smoking cessation program as a part of overall improvement of health and indeed a nurse managed smoking cessation program has proven to be more cost effective than beta- adrenergic antagonist therapy after myocardial infarction (Krumholz et al 1993).

Pregnant Women

The latest confidential enquiry into material deaths in the UK points to cardiac disease as one of the important causes of deaths in pregnancy. Considering cardiac disease in other developed countries as well, 25-50 % of these are due to Myocardial Infarction. Women with class H diabetes are more at risk. Nitrates, bed rest, oxygen, postponment of delivery for > 2 weeks, adequate analgesia with epidural for pain relief in labour and intensive monitoring will reduce the risks of deaths. There is no contraindication to the use of agents to lyse the clot. Management and treatment should be like in the case of non pregnant women. There is small but significant risk of coronary heart disease in subsequent pregnancies.

Women in Menopausal Age Group

Cardiovascular Disease and Hormone Replacement Therapy

Before the menopause coronary heart disease is uncommon in women who do not have any cardiovascular risk factors like smoking , hyperlipidaemia or diabetes. It is five times common in men than premenopausal women but once the menopause has occurred the risk of heart disease in women approaches that in men, suggesting the role of oestrogen as protective effect on the heart.

There is evidence that cardiovascular disease is a much more devastating entity where there is oestrogen deficiency. In the first year following Myocardial Infarction the mortality rate for women is 45 % more than twice that for males. Women are twice as likely as men to die within 60 days of the initial infarct, and also more likely to have second infarct.(Kannel et al 1976).

Nearly every observational study has found a decreased risk of heart disease in women whoever used oestrogen. A recent meta-analysis found a relative risk of 0.70 for coronary heart disease among women who used unopposed oestrogen and in seven studies which separately assessed oestrogen and progestogen the risk estimate was 0.66. (Barrett-Connor and Grady 1998). The aetiology of cardiovascular disease is complex and incompletely understood. Oestrogen is an antioxidant and calcium channel blocker and favourably alters lipoprotein cholesterol, plasminogen activator inhibitor and vascular reactivity. The exact mechanism of cardioprotection by oestrogen is not completely clear. Often the beneficial effect on lipid profile is translated to its cardioprotective action. It is possible that biases in the above observational studies may have spuriously increased the benefit of oestrogen on cardiovascular disease, we still have to wait for proper randomised controlled studies before we change our practice of using hormone replacement therapy.

Initial evidence from a retrospective study (Sullivan et al 1990) encouraged the use of HRT for secondary prevention of cardiovascular disease. However, Heart and Oestrogen/Progestin Replacement Study popularly known as HERS found that hormone replacement therapy did not lower the risk of having heart

attack in women who had heart disease. More recently the ERA (Oestrogen replacement and arteriosclerosis trail) study (Gottlieb 2000) failed to show any benefit after an average follow up time of 3.2 years in 309 postmenopausal women with at least one narrowed coronary artery. The worsening of heart disease was virtually same in all groups. More interestingly a small study from Mount Sinai Medical Centre, New York reported 20% reduction in the formation of blood clot in women receiving oestrogen, contradicting the popular belief of increased risk of venous thromboembolism.

Breast Cancer and Hormone Replacement therapy

Most studies (Barrett-Connor 1998) have found no increased risk of breast cancer in women who had ever had used oestrogen, usually less than two years. But, collaborative reanalysis of data from 51 epidemiological studies (Collaborative Group 1997) has shown the risk of breast cancer increases with long term (usually more than 5 years) oestrogen use. Women taking oestrogen tend to have early stage breast cancer, probably reflecting more frequent examinations and mammograms. The increased risk is not entirely explained by better surveillance and detection of more early cancers, because there is evidence for increased mortality when breast cancer is associated with oestrogen (Grodstein et al 1997) Five years after stopping the oestrogen there is no longer an increased risk of breast cancer, this probably supports the view of oestrogen as a promoter than a cause of breast cancer. In the context it may be an advantage to use Selective Estrogen Receptor Modulator or SERMS like 'raloxifene' or 'tibolone' which are agonist to bone and lipid metabolism but antagonist to breast and endometrial tissue hyper or neoplasia.

Oestrogen replacement have not shown to increase the risk of new or recurrent breast cancer in women who had breast cancer (Barret — Connor 1998). Women who have severe symptoms one year after menopause induced by chemotherapy may wish to go on oestrogen despite unknown risk. Randomised trials of oestrogen in women with breast cancer are just beginning.

Observational studies (Newcomb and Storer 1995) have found that oestrogen reduces the risk of colon cancer. A meta - analysis of 10 observational studies (Yaffe et al 1998) has shown significant protection from Alzheimer's dementia. The quality of life is also significantly improved with oestrogen replacement therapy and this is independent of complete resolution of hot flushes (Limouzin-Lamothe et al 1994).

Implications for practice

In this day and age with available evidence we can be proactive with the risk benefit ratio of oestrogen replacement. Overall more women die of cardiovascular diseases than breast cancer, however deaths tend to be later. In women under 65 breast cancer is more common than heart disease. Breast cancer is an emotive issue among women and typically women in perimenopause will have friends in their age group with breast cancer, not with heart disease. This probably explains why with lifetime favourable risk/benefit ratio coupled with even small increased risk of breast cancer is unacceptable in most women. Newer treatment with SERMS or phytoestrogens may preserve bone without increased risk of cancer and their cardiovascular effect appears to be favourable and results of large studies are awaited to confirm the findings.

Research related to Cancer

The overall prognosis for women with advanced stages of gynaecological cancer remains poor. The possibility of reducing mortality by screening for preinvasive or preclinical disease remains attractive. Much research has been directed to this aspect and has seen emergence of some new technologies.

Cervical Cancer

Oncogenic HPV types are key aetiological factor in cervical intraepethelial neoplasia and molecular HPV detection appears to be at least as sensitive as cytology for detection of high grade lesions. (Sigurdsson et al 1997).

Some HPV16 variants confer up to 6 fold increased risk of CIN 2-3 compared with other HPV variants. HPV testing has yet to enter routine clinical practice.

Automated Pap Smear

The Papnet system identified 10% of abnormalities in a panel of 487 false negative smears from 228 women with high grade CIN or cancer (Koss et al, 1997) Papnet has been investigated as a reassuring too for quality assurance. Research is on the way and evidence is now accumulating that this technology is more sensitive than manually read Pap smears. It will take time to replace manual assessment.

Research in molecular techniques

The enzyme telomerase is active in most cancer cells. Preliminary evidence suggests that telomerase may be a useful adjunct in the interpretation of Pap smears (Kyo et al 1997) and cervical biopsies as telomerase activity correlates with the sensitivity of dysplasia. Research with infra red technology as an adjunct to reduce false negative cervical smear is ongoing (personal communications). If it is proven to be valuable the women can be given the result before they leave the clinic.

Ovarian Cancer

Mutations BRCA1 and BRCA2 predispose to breast and ovarian cancer and mutations of DNA mismatch repair genes predispose to hereditary non-polyposis colorectal cancer often associated with edometrial and ovarian cancer. Women carrying BRCA1 & BRCA2 genes are though to have lifetime risk of developing breast cancer of 80 % compared to 8 % in general population. The life time risk of developing ovarian carcinoma is 45 % for BRCA1 & 25 % BRCA2. It is now possible to detect the mutant gene. However variable penetrance causes a problem for accurate prediction. Gene mutation probably accounts for less than 10 % of ovarian and breast cancer. At present mutation testing may be offered to individuals with two or more first degree relatives with ovarian or premenopausal breast cancer. Failure to find gene cell mutation in affected member of the family does not indicate that family is at a low risk, we can be proactive and recommend combined contraceptive pill to first degree relative of affected women, as they may reduce the risk of ovarian cancer by 50%. (Narod et al 1998). CA125 and pelvic ultrasound scan has been studied in a selected population. (Jacobs et al 1999). However until results are available from larger randomised trials, population screening for early detection of ovarian cancer cannot be recommended.

Endometrial Cancer

Polymerase chain reaction (PCR) can amplify minute quantities of DNA. No universal gynaecological marker has been indentified. K-ras oncogene mutations in cervical smears taken prior to clinical presentation of endometrial cancer implies screening may be feasible using molecular markers present at very low concentrations(Al-Jehnai et al 1998).

Research related to myocardial infarction:

Coronary artery disease seems to be programmed from birth or more specifically at intrauterine life. Higher prevalence of cardiovascular disease, non insulin dependant diabetes and possibly cancer, in adult life has been reported with clinical history of reduced size at birth (Leon 1998, Botero & Lifshitz 1999). Improvement of health and nutrition of expectant mothers should improve chronic disease in later life. In the UK the highest recorded rates of coronary heart disease mortality are in people born in the subcontinent countries of India, Pakistan and Bangladesh. The standardised mortality rate for South Asian men is 40% higher than the whole population and the comparable figure for women is 51%(Factfile,British Heart Foundation,2000).Although South Asians are heterogenenous group in relation to social custom and risk factors there may exist a common genetic influence which can increase the susceptibilty of individual to cardiovascular disease. Genetic influence at birth on umbilical cord plasma lipids and apolipoprotein levels of Indian and Chines newborns has been studied at National

University of Singapore (Low et al 1998). Lipoprotein Lipase (LPL) plays a critical role in the determination of plasma lipid and lipoprotein profile.With its pivotal role in lipoprotein metabolism, it is a rate limiting enzyme that controls the clearance of trigycerides, VLDL and chlomycrons from the circulation. The LPL gene has been found to be located at the short arm of chromosome 8 and the gene strucure has been elucidated. The above study showed a significant higher levels of HDL-Cholestrol level and lower level of LDL-Cholesterol among the Chinese newborns than Indian newborns.There was an association between LPL gene expression and the plasma lipid levels. Higher plasma levels of triglycerides, LDL cholestrol were found in Indian newborns with negative gene expression (P-P —genotype) than with lipoprotein gene expression (P + P + genotype). Studies have shown the association of DNA polymorphisms at the lipoprotein lipase gene to the severity of coronary artery disease and diabetes(Wang et al 1996).We hope to extend these studies to look at the ethnic, birth weight and infant feeding practices to the possible predisposition to coronary heart disease in old age.

Management options for Myocardial infarction are mainly medical and supportive in nature. Surgical options of angioplasty or coronary bypass endarterectomy are of value but does not cure every patient due to place and extent of the infarct. At end stage heart failure cardiac transplantation remains the only therapeutic modality which offers significant improvement in quality of life and survival. However there is shortage of donor heart and problem with rejection. Transplantation of foetal cardiomyoctes to circumvent the problem of terminally differentiated adult heart have recently been investigated. Foetal myocardiocytes either from foetal myocardial cell culture or from embryonic stem cells can be transferred to an affected heart. These embryonic cells are induced to become future cardiomyocytes. Results on animal experiments and early research in embryonic stem cells show promise.Transplantation of foetal cardiomyocytes and its subsequent neovascularisation is an attractive alternative to conventional surgery particularly in areas where coronary bypass surgery is not very useful. The production of these cells and subsequent transplantation need further research within ethical boundaries.

Conclusion

Cardiovascular disease and cancer are the two main causes of premature deaths. As we claim to look after half of the human race our practice should make an endeavour to reduce the causes of premature mortality and morbidity on the basis of available evidence.Our research is directed towards early detection of gynaecological cancers & looking at new avenues for treatment of myocardial infarction.By being pro-active in our speciality we can practice and carry out our research beyond boundaries to respond to our national priority.

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