Gynaecological Oncology Society, Maternal and Fetal Society and Update meetings

CSIR, Pretoria, May 2009

Gynaecological Oncology Society Meeting

Thursday 21 May 2009

THE PLACE OF LAPAROSCOPIC LYMPHADENECTOMY IN GYNAECOLOGICAL CANCER

Prof. Leon Snyman

University of Pretoria

The first limited laparoscopic lymphadenectomy was performed in 1989. Since then, several publications have reported on the feasibility, safety and validity of this procedure in several gynaecological cancers. The current literature on this subject comprises mainly observational studies. Available evidence suggests that this procedure is safe.

Advantages include less blood loss, shorter hospital stay, a shorter recovery period, and reduction in total cost. Laparoscopic lymphadenectomy has a place in the staging as well as the treatment of different gynaecological cancers, mainly cervical and endometrial cancer.

Recurrence risk as well as port site metastases are important considerations that will be alluded to in this discussion. We will also discuss the different options of lympadenectomy, including extraperitoneal lymph node dissection.

Laparoscopic surgery now forms part of the armamentarium of the modern gynaecological oncologist. The challenge we face in this regard is acquiring the necessary skills in order to be able to perform this type of surgery safely in gynaecological oncology.

SCREENING FOR OVARIAN CANCER

Dr D Oram

Ovarian cancer is a disease characterised by a complete lack of consistent, reliable, early symptomatology and as a result is encountered at an advanced stage at the time of presentation in over 75% of cases. Overall 5-year survival rates are variously quoted between 20% and at best 30%. However, in the minority of cases that are diagnosed when the disease is confined to the ovaries, 5-year survival rates in excess of 80% are described, the figure rising to over 90% for stage IA disease. The rationale underlying the quest for developing a screening strategy in ovarian cancer is therefore to try to achieve down-staging of the disease at the time of detection on the assumption that earlier diagnosis will have a positive impact on mortality figures.

Data from a 30-year research programme will be presented. This will include an evaluation of the two main screening tests used in this disease, CA125 and transvaginal ultrasound. The results of the first-ever randomised controlled trial involving 22 000 women using CA125 and ultrasound in a sequential multimodal fashion will be discussed.

The development of a mathematical algorithm, the Risk of Ovarian Cancer (ROC) algorithm, which allows CA125 to be used in a more sophisticated fashion with improved specificity and sensitivity, will be presented. The case will then be made for the performance of a large-scale, multicentre, randomised controlled trial of screening for ovarian cancer.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) involving 200 000 women in 13 participating centres will be described. Recruitment in this trial was completed in 2005 with 50 000 women being randomly allocated to a multimodal arm including primary screening with serum CA125. A further 50 000 women were randomised to screening using transvaginal ultrasound, a final 100 000 women being randomised to a control arm where no screening was undertaken but annual follow-up is maintained. The results of prevalence screening in this the world's largest trial of ovarian cancer screening will then be presented.

CURRENT STANDARDS OF MANAGEMENT OF PREMALIGNANT GENITAL DISEASE

Prof. B G Lindeque

University of Pretoria

Premalignant lesions of the cervix are common and are usually detected by cytology. The most commonly used form of therapy is a colposcopic-assisted LLETZ procedure. The success rate is as high as 95% and the most important reasons for recurrence are unsatisfactory colposcopy, involved margins at the time of LLETZ, and postmenopausal age group. The best predictor of recurrence however is positive HPV testing at first follow-up.

The use of cone biopsy or hysterectomy is still acceptable for dealing with HSIL lesions. In the case of hysterectomy some histological confirmation is required prior to the

hysterectomy to decrease the chances of inadvertent intra- or postoperative finding of invasive cervical cancer.

There is however a new debate: should a policy be implemented of cryotherapy at the time of visual inspection of the cervix (with acetic acid) (VIA)? VIA has gained popularity around the world as a way of detecting cervical abnormalities in a low technological manner. Macroscopically detectable frank cancers must clearly be referred for specialist treatment. The finding of a white lesion on VIA in a clinic setting can be followed more easily by immediate cryotherapy than LLETZ. The advantages and disadvantages are being studied and must be debated.

Vulvar premalignancy occurs less commonly than SIL lesions but may involve patients with HIV infection as well. Detected VIN is probably not dangerous as simple management (excision) will usually result in no further progression of the disease. Undetected VIN is clearly more important. Recurrent VIN will require recurrent excision. Recent reports suggest success for imiqomod as treatment for VIN.

Vaginal intraepithelial neoplasia is rarely found in a patient with no history of SIL lesions. It is a cytological diagnosis and needs colposcopic assessment. If a lesion is visualised it should be excised. If multiple lesions are present or in HIV-infected persons consideration should be given to the use of 5-FU direct contact treatment.

Some patients with VIN will also have anal intraepithelial neoplasia, a difficult disorder to diagnose, evaluate and treat.

PRIMARY FALLOPIAN TUBE CARCINOMA

Dr M H Botha

Stellenbosch University

Primary fallopian tube carcinoma is one of the least common diagnoses in gynaecological oncology. Information about this rare condition is limited to fairly small case series and well-researched clinical guidelines are not available.

The diagnostic criteria for the diagnosis of a primary fallopian tube cancer state that the tumour should arise from the endosalpinx, the histological pattern should reproduce the epithelium of the tubal mucosa, transition from benign to malignant epithelium is found on histology, and the ovaries are either normal or have smaller tumours than that of the tube. The classic symptoms include a serosanguinous discharge, pain and an adnexal mass, but other symptoms are also present regularly. These include vaginal bleeding (up to 35%), offensive vaginal discharge and abdominal distension. Imaging and CA125 may aid in the diagnostic work-up. Staging is according to the FIGO system.

Management is similar to that of ovarian carcinoma. Surgical debulking and adjuvant chemotherapy is the preferred treatment and radiotherapy may play a limited role in selected cases.

Owing to the small number of cases, prospective randomised studies to determine the treatment of choice will remain difficult. Management of this condition should be done by multidisciplinary teams, preferably in tertiary referral centres.

IMPACT OF CONTRACEPTION AND HIV STATUS ON CERVICAL CARCINOGENESIS

Dr M Moodley

University of KwaZulu-Natal

High-risk human papillomavirus (HR-HPV) is the necessary causative agent for the development of cervical cancer. However, the mere presence of HR-HPV in itself is insufficient as other co-factors are required for the full expression of the malignant phenotype. Such co-factors include steroid contraception and immunodeficiency (HIV). The role of steroids in cervical carcinogenesis has been reported since 1977, with all types of steroids being implicated. In relation to never-users, women who used oral contraception (OC) for less than 5 years did not have an increased risk of cervical cancer (OR 0.66; 95% CI 0.45 - 0.98). The OR for OC use was 2.32 for 5 - 9 years of use and 4.03 for use of 10 years or more. In 2003, the international collaboration of epidemiological studies of cervical cancer evaluated 24 studies of OC use and cervical cancer comprising 16 573 women with cervical cancer and 35 509 women without cervical cancer from 26 countries. Relative risks calculated included duration of use as well as time since last use. Users of OC of less than 5 years had no significant increase in cervical cancer. Users of of OCs for 5 years or more had almost twice the risk compared with non-users (RR 1.99; CI 1.69 - 2.13). Each year of OC use was associated with a change in risk factor of 1.07. Ten years of use of OC from age 20 to 30 years increased the cumulative incidence of cervical cancer by age 50 from 7.3 to 8.3 per 1 000 in less developed countries and from 3.8 to 4.5 per 1 000 in more developed countries. However, most of the data are derived from countries where screening was sub-optimal or non-existent. It is thought that the additional absolute risk of cervical cancer due to OC use in well-screened populations is likely to be lower. Based purely on epidemiological evidence, the IARC (2005) re-classified steroid contraceptives as a class 1 cancer-causing agent. However, a subsequent correspondence from the IARC stated that there should probably be no change in prescribing patterns in view of the benefits (reduced maternal mortality) versus the risks of OCs. The Centers for Disease Control (CDC), USA, labelled cervical cancer an AIDS-defining illness in 1993. The issue, however, is complex and studies have not clearly demonstrated any significant increase in cervical cancer, especially in Africa. HIV-infected women with high-risk HPV types were 40 times more likely to have a cervical cancer precursor lesion than women not infected with the HPV or HIV viruses. While clear evidence of an increased prevalence of cervical cancer in association with HIV has not been demonstrated, conversely, the incidence of cervical cancer has actually dropped in less-developed countries possibly due to the higher mortality from HIV/AIDS-related illnesses and shorter lifespan.

TRACHELECTOMY

Prof. Greta Dreyer

University of Pretoria

The aim of this paper is to give an overview of this new surgical treatment modality.

Definition. Trachelectomy and radical trachelectomy is a term used for the vaginal or abdominal removal of the

uterine cervix with or without the para-cervical ligaments for the treatment of malignancies of the cervix. The procedure can be done together with open or laparoscopic pelvic lymph node dissection.

Indications. The radicality needed for the complete removal of the cervical malignancy is identical whether or not the uterus is removed with it. This radicality refers to removal of the vaginal cuff and the para-cervical ligaments and the tissue around the vascular supply. This is determined by the size, stage, tumour type, depth of invasion and lymphovascular invasion; the same factors that also determine the need for lymph node dissection.

However, the uterus cannot be safely saved if there is deep invasion of the cervical stroma, if the tumour is more than 2 cm in size or when the cutting edge on the isthmus is not at least 5 mm from the nearest tumour (probably more for adenocarcinoma). Adjuvant pelvic radiation will render the uterus and pelvic ovaries useless for reproduction.

Disease outcome. If all the rules are followed and suitable surgery is performed, the risk for recurrence on the remaining uterine isthmus is very small. Comparable patients have very early-stage disease and hence an excellent survival after classic radical hysterectomy. This is difficult to match with lesser surgery. Reported series contain widely varying patient populations, but invariably report excellent outcomes. Many of the early series include patients who could have been safely treated with old-fashioned cone biopsy.

Pregnancy outcome. This exciting development offers many women the chance to have curative surgery while retaining childbearing ability. Many babies have been born after trachelectomy or radical trachelectomy and fertility seems almost unchanged. The main pregnancy complications are premature rupture of membranes, prematurity and infections.

Maternal and Fetal Society Meeting

21 May 2009

THE ROLE OF DOPPLER IN IUGR

Prof. Jim Dornan

It is almost 30 years since the first abnormal umbilical artery wave forms were displayed by Drumm and his colleagues. Now, three decades later, we continue to recognise the importance of the assessment of flow, and wave form analysis of the maternal uterine artery and many fetal vessels in helping us to assess the physiology and pathology of the fetus. Deciding what to look for, when and where, and delineating their importance is sometimes highly scientific, and sometimes an art form.

Doppler of uterine arteries is used in many units to screen the normal population in order to identify a high-risk group where they have closer surveillance. The use of umbilical arteries and mid-cerebral artery assessment in potential fetal compromise, and the latter in rhesus disease, is assured. However, there is still much careful evidence to be gathered and shared with the obstetric community, and at a time of increased access to Doppler apparatus but not necessarily an increased understanding of how to interpret the data produced.

LESSONS LEARNT FROM A LOCAL AUDIT OF THE PRENATAL DIAGNOSIS OF ANEUPLOIDY

Dr L Geerts

Stellenbosch University

Introduction. To identify pregnancies at high risk of aneuploidy, maternal age is often the only selection criterion used. This study compares the efficacy and efficiency of an opportunistic ultrasound-based risk assessment (risk cut-off of 1 in 200) to a maternal age cut-off of 37 years.

Methods. This was a retrospective study of all chromosomal abnormalities diagnosed perinatally in the Human Genetics Laboratory (Tygerberg Hospital) from 1.1.2003 to 31.12.2005. Aneuploidy risk was calculated by combining maternal age and ultrasound findings according to the Fetal Medicine Foundation algorithm. Chi-square tests were used to compare screening performance of both strategies.

Results. Chromosomal abnormalities were detected in 136 perinatal karyotype samples (46 prenatal, 90 postnatal), with maternal age known in 104 women (76.5%) and ultrasound-based screening results in 64 (47%).

Of the 130 **clinically relevant aneuploidies**, 60 underwent assessment by ultrasound (46.2%). Of these, 54 had ultrasound abnormalities (90%) and 55 screened high risk (91.7%).

Of the 114 fetuses with **autosomal trisomy** (71 trisomy 21), maternal age was known in 86 and 48 mothers were younger than 37 years at conception (55.8%). Ultrasound assessment was done in 49 (43%) and 46 had abnormal findings and screened high risk (93.9%). The detected abnormalities were multiple in all but 2 cases.

The ultrasound-based approach had a higher sensitivity than maternal age for all major chromosomal abnormalities (94.8% v. 41.2%, $p<0.001$), for all autosomal trisomies (93.9% v. 44.2%, $p<0.001$) and specifically for trisomy 21 (93.1% v. 43.8%, $p<0.0001$).

Of the 9 662 women seen in the ultrasound unit during the 3-year period (0.66% background incidence for all chromosomal abnormalities ($N=64$)) karyotyping was performed in 915 (9.5%) and 5% of results were abnormal (46/921). The positive predictive value of advanced maternal age in this cohort was 2.2% (29/1 310); the false positive rate was 1.9% (1 285/1 310). Twenty of 685 prenatal samples from older women (2.9%=1:34.3) were abnormal compared with 26 of 230 samples from younger women with high-risk results (11.3%=1:9.4) (OR 0.24; 95% CI 0.12 - 0.45; $p<0.001$) (for autosomal trisomies 1: 42.8 v. 1:13.5, $p<0.001$). Offering karyotyping to younger women improved the prenatal diagnosis of all chromosomal abnormalities by 130% (46 instead of 20) and of autosomal trisomies by 106% (33 instead of 16).

Postnatal diagnosis was mainly (80%) due to lack of prenatal ultrasound assessment.

Conclusion. Regarding the prenatal detection of aneuploidy, the efficacy and efficiency of ultrasound-based risk assessment were far superior to screening by maternal

age alone. Universal ultrasound-based risk assessment is therefore advocated, with invasive testing services based on risk result rather than the currently used empiric age cut-off. This will have many advantages in a resource-poor setting such as South Africa.

LATE TERMINATION OF PREGNANCY BY INTRACARDIAC POTASSIUM CHLORIDE INJECTION AT A TERTIARY REFERRAL CENTRE

Dr L Govender

University of KwaZulu-Natal

Objectives. To report on our experience with intracardiac potassium chloride (KCl) injection as a method of feticide for severe congenital abnormalities and to analyse the indications and acceptance for termination of pregnancy (TOP) beyond 24 weeks' gestation.

Method. This study was a retrospective review of the hospital records of women who were offered late TOP (≥24 weeks) for severe congenital abnormalities during the period August 2003 - October 2008 at the Fetal Medicine Unit of a tertiary/quaternary referral hospital in KwaZulu-Natal. This unit has established guidelines for late TOP. The patient demographics and types of fetal anomalies were analysed according to the groups that accepted or declined late TOP. We also report on our experience with intracardiac KCl injection as the method of feticide. SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) was used for analysis of the data. Descriptive statistics were used for the distribution of data and Pearson's chi-square tests for the comparison between groups. A p-value <0.05 was considered statistically significant.

Results. During the study period 3 896 women were seen and of these 2 209 women were at ≥24 weeks' gestation at their first visit. Severe congenital abnormalities necessitating late TOP were offered to 253 women (study group) of whom 191 (75%) accepted. The differences in the maternal age, parity, race, gestational age at diagnosis and level of the referring hospital between the groups were not statistically significant. Similarly, there was no significant difference between the groups for the types of fetal abnormalities. The most frequent indication for late TOP was brain abnormalities (38%), followed by spine (20%) and aneuploidy (14%). Hydrocephalus was the commonest CNS anomaly. Fifty-three women who accepted late TOP did not undergo feticide for a variety of reasons. Feticide by intracardiac KCl injection was performed in 138/191 (72%) cases of which 87(63%) were beyond 30 weeks' gestation. The feticides performed per category were as follows: CNS 64, NTD 22, aneuploidy 19, multiple fetal abnormalities 17, skeletal 6, twin anomalies 5, cardiac 3 and renal 2. Cephalocentesis was performed at the same setting in 18 cases. The mean difference in time from diagnosis to performance of feticide was 10 days (range 0 - 42 days). Fetal asystole was achieved in all cases by a single needle insertion within 2 minutes of intracardiac KCl injection with median volumes of 8 ml (5 - 10 ml) at 24 - 25 weeks, 10 ml (5 - 12 ml) at 26 - 30 weeks and 14 ml (8 - 16 ml) at >30 weeks (p=0.001). The mean duration of the procedure was 12 minutes (6 - 25 min). No maternal complications occurred during the procedure. Stillbirths were confirmed in all cases.

Conclusion. The majority of women in our study opted for late TOP for severe fetal abnormalities. Intracardiac KCl administered under direct vision induces immediate asystole and appears to be a relatively safe and effective method for late TOP.

PERINATAL MORTALITY DUE TO DIABETES MELLITUS RECORDED WITH THE PERINATAL PROBLEM IDENTIFICATION PROGRAM (PPIP) IN SOUTH AFRICA

Dr Hennie Lombaard

University of Pretoria

Prof. Robert C Pattinson

University of Pretoria

Aim. The aim was to study the perinatal mortality rate due to diabetes mellitus (DM) in sites throughout South Africa that use the Perinatal Problem Identification Program (PPIP).

Methods. South Africa is a developing country. The PPIP data from 1 January 2000 to 31 December 2007 were analysed. PIPP was started in 2000 and at that stage included 27 sites, which were regional and level 3 hospitals throughout South Africa. PPIP is constantly expanding in South Africa. In 2007 180 health care centres took part in the PPIP audit. All the centres are from the public health sector. The sites are distributed through the metropolitan, urban and rural areas in South Africa. As the programme expanded it included midwife obstetric units (MOUs) in South Africa. During the period 2006 and 2007 the programme covered 40% of deliveries in South Africa. These are institutional data from voluntary sites taking part in the PPIP audit. The perinatal mortality rate was calculated for all deaths that were found to be due to diabetes mellitus. Diabetes mellitus is inclusive of type 1 DM, type 2 DM and gestational diabetes mellitus (GDM). The study also evaluated the perinatal mortality from unexplained stillbirths weighing more than 4 kg. The perinatal mortality rate is expressed per 1 000 deliveries.

Results. From 1 January 2000 to 31 December 2007 a total of 1 809 347 deliveries were recorded in the PPIP sites. In total there were 373 deaths recorded due to DM. Of infants whose deaths were related to DM, 96 had a birth weight of more than 4 kg. Over this period there 192 unexplained stillbirths with a birth weight of more than 4 kg. The perinatal mortality rate (PMNR) is presented in Table I (p...). The sum is the perinatal mortality rate for DM and unexplained stillbirths weighing more that is combined.

Since 2002 there has been a steady incline in the perinatal mortality rate due to DM in South Africa. We were unable to calculate a perinatal mortality rate specific for women with DM.

Conclusion. Since 2002 there has been a steady incline in the perinatal mortality due to DM. The decline from 2000 until 2002 is probably due to the inclusion of MOUs and not a true decline in the perinatal mortality rate. In South Africa we are not meeting the St Vincent Declaration.

SCREENING FOR PRE-ECLAMPSIA

Dr S Mahsud-Dornan

University of Belfast

Pre-eclampsia is the third biggest killer of women in the world. In its later, clinically overt stages it is diagnosable and readily treatable where resources permit.

Table I. Perinatal mortality due to DM in PPIP sites in South Africa

Years	2000	2001	2002	2003	2004	2005	2006	2007
Total deliveries	62 931	88 306	164 144	254 294	265 991	315 344	362 041	297 768
PNMR (DM)	0.485	0.336	0.196	0.290	0.202	0.259	0.272	0.277
PNMR (IUD>4)	0.039	0.129	0.084	0.124	0.109	0.121	0.195	0.182
Sum	0.524	0.465	0.280	0.414	0.311	0.380	0.467	0.458

Defective trophoblastic invasion in early pregnancy is known to occur and is associated with subsequent development of pre-eclampsia, IUGR and other pregnancy complications. In these pregnancies the uteroplacental circulation remains in the state of high resistance and low flow, which can be measured by Doppler ultrasound.

There is also at least one biochemical, so far unidentified, factor associated with endothelial damage, which suggests the potential for the detection of a biomarker, or biomarkers, that could predate the clinical disease and thus permit treatment and preventive strategies to be assessed.

Six of these biomarkers were studied, using ELISA, at 20 weeks gestation, from a cohort of 671 primigravidas. Twelve developed severe pre-eclampsia and 30 IUGR. There were no significant findings with VEGF (RIA also used), sFlt, activin A, selectin or leptin.

Inhibin A had the maximum classifying ability to discriminate between placental dysfunctions and normal mothers. ROC analysis revealed that inhibin A had 77 times more predictive ability in identifying placental insufficiency compared with the other five factors. The negative predictive values were also significant for inhibin A, suggesting a role in the identification of a low-risk group of mothers.

Recent work suggests that first-trimester Doppler studies, allied with maternal biomarkers, warrants further investigation and appears to offer the most rewarding prospect of prediction of pre-eclampsia at this time.

The first trimester would also be the most logical time for the likely success of a potential pharmacological intervention that could lessen, or indeed prevent, the effects of the condition.

DO EARLY AND LATE PRE-ECLAMPSIA SHARE THE SAME AETIOLOGY? WHAT DOES THE PLACENTA REVEAL?

Dr J L van der Merwe

Stellenbosch University

Introduction. To investigate whether differences exist between placentas from early- and late-onset pre-eclampsia as well as between late-onset pre-eclampsia and normal term deliveries.

Methods. Prospective case series with continuous data capture. 100 women were studied: 25 with early- and 25 with late-onset pre-eclampsia. Both of these groups had an equal number of controls matched for gestational age. Placentas underwent routine preparation. They were evaluated twice by 2 independent pathologists in a strictly predetermined, standardised manner. The first evaluation was without clinical information or sub-group allocation, while the second evaluation was preformed after disclosure of the gestational age at delivery.

Setting. Tygerberg Hospital, a secondary and tertiary referral centre in the Western Cape province of South Africa.

Results. Placentas in the early pre-eclampsia group were smaller ($p<0.01$), had more infarctions (OR 4.03, 95%CI 1.2 - 13.5), less appropriate maturation (OR 16.62, 95%CI 4.1 - 68.0) and more nucleated red blood cells (12% v. 0%). The only differences between placentas from the late-onset pre-eclampsia and uncomplicated term groups were more decidual arteriopathy (OR 5.09, 95%CI 1.45 - 17.92) and abruptio placentae (OR 5.41, 95%CI 1.01 - 28.79) in the pre-eclampsia group.

Conclusions. Clear differences were seen between the early- and late-onset pre-eclampsia placentas, while late-onset pre-eclampsia and normal term placentas differed less. These findings support the notion that early- and late-onset pre-eclampsia are different clinicopathological entities.

PROGESTERONE AND PRETERM LABOUR

Prof. David Hall

Stellenbosch University

Preterm labour and birth are major challenges in both developing and developed countries. The risks associated with preterm birth include death, severe neurological deficits and sepsis. The treatment and support required by these complications translate into major health care expenditure.

Because prevention of preterm labour has been so elusive, much attention has focused on early diagnosis and treatment. Of the options for prevention, progesterone has remained the most promising. This hormone prevents the formation of gap junctions and inhibits myometrial contractions and cervical ripening.

Prior to 2000, opinion was divided, but a number of robust trials have been completed since then. Current systematic reviews and position statements are cautiously endorsing the prophylactic use of progesterone. It is important to correctly identify the population most likely to benefit from this prolonged intervention. At present there is no consensus on the dose or route of the medication.

OVERVIEW OF IUGR

Prof. Jim Dornan

Panellists: Prof. Hein Odendaal and Prof. Bob Pattinson

The fetus that does not reach its growth potential is at increased risk of malnutrition, leading to head sparing, leading to cerebral damage, coma, stillbirth, neonatal morbidity, and the early onset of adult vascular diseases such as diabetes and ischaemic heart disease.

We have a very poor record of detecting IUGR antenatally, yet we know that if it is detected in time, appropriate timely delivery can be arranged, and correct neonatal nutritional supplements implemented. There is, however, still much work to be done on:

1. Aetiology of IUGR
2. Detection of IUGR
3. Prevention of IUGR
4. Treatment of IUGR
5. Management of IUGR.

Only in the last section have we made satisfactory progress in the last 20 years.

IUGR is now recognised as the biggest preventable aetiological cause of stillbirth, and eventual premature death. It is highly likely that it is eventually preventable. Meanwhile we will have to do with improving detection antenatally, as at least we know what to do with them once we know they are there.

Let's discuss.

O&G Update 2009

22 and 23 May 2009

INJECTABLE CONTRACEPTIVES IN SOUTH AFRICA: SHOULD THEY STILL BE USED?

Jack Biko

Pretoria University

Depot medroxyprogesterone acetate (Depo) and norethisterone enanthate are among the commonest freely available contraceptives, and are routinely provided by the state clinics in South Africa. Postpartum patients are always offered Depo before they are discharged home.

The reported negative effects of Depo include weight gain, bone loss, abnormal uterine bleeding and delayed return to fertility. Some studies in Africa suggest that progression of HIV disease is increased in hormonal contraceptive users compared with non-users. This is especially the case in high-risk women. However, use of hormonal contraceptives in HIV-infected women is classified by the World Health Organization (WHO) as category 1 (use the method in any circumstances), while use of hormonal contraceptives in women on antiretroviral drugs is listed as category 2.

The effects of pregnancy on weight gain and bone loss by far exceed those ascribed to Depo. The complications of unplanned pregnancy include septic abortions and maternal death. The reported negative effects of Depo are reversible and manageable. Depot medroxyprogesterone acetate and noresthiterone enanthate are generally safe and well tolerated.

SCREENING FOR OVARIAN CANCER

Dr D Oram

Ovarian cancer is a disease characterised by a complete lack of consistent, reliable, early symptomatology and as a result is encountered at an advanced stage at the time of presentation in over 75% of cases. Overall 5-year survival rates are variously quoted between 20% and at best 30%. However, in the minority of cases that are diagnosed when the disease is confined to the ovaries, 5-year survival rates in excess of 80% are described, the figure rising to over 90% for stage IA disease. The rationale underlying the quest for developing a screening strategy in ovarian cancer is therefore to try to achieve down-staging of the disease at the time of detection on the assumption that earlier diagnosis will have a positive impact on mortality figures.

Data from a 30-year research programme will be presented. This will include an evaluation of the two main screening tests used in this disease, CA125 and transvaginal ultrasound. The results of the first-ever randomised controlled trial involving 22 000 women using CA125 and ultrasound in a sequential multimodal fashion will be discussed.

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CURRENT STATUS OF HPV TESTING AND VACCINATION

Prof. B G Lindeque

University of Pretoria

In a fast-evolving world it has become clear that new strategies have to be used to achieve important objectives. Screening for cervical cancer and its precursors remains as important in South Africa today as it has been in the past decades. One truth has become clear for all observers, however: no screening programme in Africa will ever be successful if conventional cytology is used. The logistics are too complex, and the number of screeners is too low and will not grow to reach the required capacity. For screening programmes in South Africa there must be a movement towards HPV screening. Current technology makes it possible that one technologist can control many

tests repeatedly per day, totally different from cytology. The sample can be wet or dry, can be taken by a health worker or by the patient, the results can be obtained in yes/no format or with detail on the specific HPV type that is present. Those with hrHPV present can be considered for cytology to detect SIL lesions.

Where cytology is used HPV testing remains an important adjunct in the situation of ASCUS, after treatment for HSIL and in other high-risk situations. HPV testing at too early an age will unfortunately cause anxiety as many persons with HPV detected in their teens and twenties will by natural immune responses get rid of the HPV infection.

The available vaccines against HPV 16 and 18 (and in one other case, HPV 6 and 11) have been proven over the available follow-up time to be safe and very effective. As a public health policy statement (endorsed by WHO, GAVI and many other bodies including the SA HPV Advisory Board) all girls in the population should receive the vaccine when they are between 11 and 13 years old. Debatable issues are whether boys should be vaccinated or whether the HPV vaccine can be introduced under the age of 18 months to fit with other vaccine programmes. The effectiveness of the vaccine in HIV-infected persons has not been demonstrated yet. Adult females can of course also access the vaccine although if they have had natural immunity against the HPV types included in the vaccine they will not have much added benefit. There is a factor of cross-immunisation against other HPV types found with both of the available vaccines. Vaccinated persons must still be screened throughout their lifetime although the screening interval is likely to increase.

THE PREVENTION OF OVARIAN CANCER

Dr D Oram

For as long as long-term cures of established disease with conventional treatment remain elusive, and for as long as the concept of screening and early diagnosis remains in the realms of research, the issue of possible prevention of this lethal disease remains relevant. Two aspects of prevention will be discussed: medical prevention with the oral contraceptive pill, and the primary focus of the presentation, surgical prevention both as a primary surgical procedure in defined high-risk individuals and also as a secondary opportunistic practice of prophylactic oophorectomy at the time of surgery for benign disease.

This remains a highly controversial subject that invokes strong opinions. The arguments in favour of prophylactic oophorectomy and the counter-arguments will be discussed and the risk-benefit analysis of such a procedure will be examined. A survey of the practice of prophylactic oophorectomy by Fellows and Members of the RCOG will be presented with a detailed breakdown of responses. An analysis of changing practice over a 20-year period of time will also be presented and the impact of changing attitudes towards HRT and the effect that this has on oophorectomy rates will be assessed.

RISK MANAGEMENT IN O&G – BEYOND SURGICAL TECHNIQUE

Dr Mark O'Brien

Medical Director, Cognitive Institute and MPS, Australia

Dr Graham Howarth

MPS Head Medical Services – Africa

By virtue of the combination of the underlying pathology and the difficulty and complexity of surgery, the outcome of a procedure may not meet patient expectations. If this is the case the surgeon runs the risk of an unhappy patient who initiates a whispering campaign – never nice, and difficult to control. Alternatively they may complain to the HPCSA – never pleasant even if you are totally exonerated; or the patient may decide to sue.

Most surgeons pride themselves on their surgical expertise and their risk management is often concentrated on surgical technique or other issues related to surgery. While there is no doubt that this is extremely important risk management in averting patient unhappiness and the sequelae thereof, risk management goes far beyond surgical technique. If you are an obstetrician and gynaecologist and have been complained about, you know that even good doctors get criticised and sued.

The session, given by two experts, one in the medico-legal arena and the other a doctor with expertise in doctor-patient communication, will concentrate on non-surgical risk management strategies to minimise patient unhappiness – particularly when the outcome is not what the patient had anticipated.

SOME PRACTICAL TIPS ON COMBINED ORAL CONTRACEPTIVE PILLS (COCS)

Prof. J Guillebaud

COC mortality. The incidence of colo-rectal carcinoma is significantly reduced in COC users, in addition to cancers of the breast and endometrium. COCs have their main (small) effect on every known associated cause of mortality during current use. The excess thrombotic risk has vanished by 4 weeks. By 10 years all-cause mortality in past-users equals that for never-users.

Migraine with aura, even without the COC but increased by it, is an important risk factor for ischaemic stroke, indeed it is now less sure there is any added risk in migraine without aura.

Tips for diagnosing: First establish the timing: neurological symptoms of aura begin before the headache itself, typically last around 20 - 30 minutes, max. 60 minutes, and stop before the headache (which may be very mild). Headache may start as aura is resolving or after up to one hour.

• Visual symptoms occur in 99% of true auras and hence should be asked about first.

• Typically there is a bright loss of part of the visual field on the same side in both eyes (homonymous hemianopia).

• Fortification spectra are often described, typically a scintillating zig-zag line gradually enlarging from a bright centre on one side, to form a convex C-shape surrounding the area of lost vision (which is a bright not dark scotoma).

• Sensory symptoms are highly confirmatory of aura, but occur in only about one third of cases and rarely in the absence of visual aura. Typically they come as 'pins and needles' (paraesthesia) spreading up one arm or one side of the face or the tongue; the leg is rarely affected. They are positive symptoms, not loss of motor or other neurological function (serious though that is – justifying hospital referral and stopping the COC).

• Disturbance of speech may also occur, in the form of nominal dysphasia, again confirmatory.

• Aura without headache is also in the WHO 4 category (i.e. 'Do not use') for the COC!

BUT all ethinylestradiol (EE)-free methods are acceptable for women with aura – warn that the headaches may persist, the switching is for greater safety against stroke – and will avail less if the woman continues to smoke …!

Clinical implications – taking an aura history (Anne MacGregor, personal communication):

• Ask the woman to describe a typical attack from the very beginning, including any symptoms in the hour before a headache. Listen to what she says but at the same time watch her carefully.

• A very suggestive SIGN of true aura is *if she draws something in the air to one or other side of her own head*!

In summary, aura has three main features:

1. Characteristic TIMING: onset BEFORE + duration ≤1 hour + resolution before or with onset of headache

2. Symptoms VISUAL (99%)

3. Description VISIBLE (using her hand).

Prescribing. In 1996 an international consensus meeting stated 'there are only two prerequisites for the safe provision of COCs': a careful personal and family history to identify all cardiovascular risk factors including migraine, and a well-taken blood pressure. There was (only) one other pre-requisite they should *also* have highlighted, the BMI, since *a BMI of anything above 30 is WHO 3 (meaning an alternative is always preferred), and above 40 is WHO 4*. Routine screening by any blood test, and breast/bimanual examinations, are however irrelevant to the COC *per se*, and should be done only if clinically indicated in that woman's case. It is good practice, after say 12 - 15 months of more frequent follow-up, for healthy users with no problems and a good blood pressure, to *provide one year's supply* at a time (i.e. 12 - 13 packs!) – as now advised by WHO.

Intercurrent diseases. It is impossible to list every known disease that might have a bearing on COC prescription, and for many the relevant usage data do not exist. A working rule therefore is to ascertain whether or not the condition might lead to *summation* with known major adverse effects of COCs, particularly with the risk of any circulatory disease. If not, COCs are WHO 2 (*benefits outweigh risks*), though even so one should be alert for the onset of new risk factors. Reliable protection from pregnancy is often particularly important in these cases. *NB: Beware, again, the thrombogenic dis-ease of OBESITY …*

Counselling should be backed by a good leaflet. Few are good on the issue of 'missed tablets'. In the UK most currently give the WHO advice for 20 µg pills whatever the COC. This caution is only logical, given the huge between-women variability of ovulation suppression with any strength of pill and the crucial importance of not lengthening the pill-free interval (PFI).

In summary, instructions should make 3 simple points:

1. *Whenever* 'more than one tablet missed', now meaning >24 hours late, USE CONDOMS as well for 7 days, +

2. If any pill missed *in the 3rd active pill week*, RUN ON to the next pack (skip any placebos), +

3. *In 1st week emergency contraception (EC) needed IF*, with sexual exposure since last pack, she is a 'LATE RESTARTER' by > 2 days (> 9 days duration of the PFI) or has missed >2 of the first-week pills.

What if there were to be no pill-free intervals (PFIs) at all? Missed-pill advice would boil down to one instruction, to use condoms for 7 days once about 5 pills were missed! Many women prefer long-term COC-related amenorrhoea, once convinced it is medically acceptable. Also cyclical symptoms (the regular bleeds themselves, PFI-linked headaches and the PMS that some COC users report) would be reduced. Hence the new enthusiasm for *continuous* 365/365 *pill-taking*. Surprisingly, very *low*-dose (20 µg) pills seem to work best – and Lybrel (continuous EE 20/LNG 90) is already on some markets. So a pill-taker *may choose this option now*, with this or any 20 µg COC, *on an unlicensed/'named patient' use basis*, but she needs warning that light (usually) but very unpredictable spotting occurs – especially in the early months. If the duration of such loss exceeds 4 days she is advised to take a 'tailored' (to her) PFI, of either 3 or 4 days. This gives her what might be termed a brief pharmacological curettage, after which with resumed pill-taking amenorrhoea should return.

THE LEVONORGESTREL-IUD AND RELATED PROGESTOGENS

Prof. J S Bagratee

University of KwaZulu-Natal

Progestogens may prevent pregnancy in various ways: by suppression of ovulation, by making cervical mucus hostile, by suppression of cyclical development of the endometrium and by delaying ovum transport. They may be administered as long-acting contraceptive agents by incorporation in sustained-release systems. These include the injectables, implants, once-a-month pills, vaginal rings and progesterone-releasing intrauterine devices (IUDs).

There are three implantable contraceptives available: Norplant, Implanon and Jadelle. Implanon is a single-rod implant with a length of 40 mm and a diameter of 2 mm, which is applied subdermally with a disposable sterile inserter. It contains approximately 68 mg 3-ketodesogestrel or etonorgestrel (ENG). The initial release rate of the implant is about 67 µg/day, which decreases slowly over time. This results in a plasma ENG concentration of >90 pg/ml, which inhibits ovulation for at least 3 years. In an Indonesian study, the continuation rate after 1 and 3 years was 97.3 and 90.6/100 women, respectively.

Vaginal rings provide good contraceptive effect through the constant release of small amounts of steroids, thereby avoiding the first-pass hepatic effect. The system developed by the WHO releases 20 µg levonorgestrel (LNG)/day, providing a constant blood level for at least 3 months. It is used continuously and is removed during menstruation. The discontinuation rate for bleeding irregularities was 15.7 per 100 women at 390 days of use.

The levonorgestrel (LNG)-IUD (LNG-IUD) combines the advantages of hormonal and intrauterine contraception.

The LNG-IUD has the same low pregnancy rate in every age group of users, in contrast to the failure rate of copper-releasing IUDs as well as other methods of fertility regulation, which is higher in young women and decreases with age. The Pearl pregnancy rate in studies has been 0.0 - 0.2 per 100 women years. It also has non-contraceptive health benefits. It is effective in the treatment of menorrhagia and is a good alternative to hysterectomy. Endometrial suppression by LNG results in a significant reduction of menstrual blood loss or amenorrhoea. During the first year of use, it reduced menstrual blood loss by 90% from pretreatment levels. It may be used for up to 5 years and there is a rapid return of fertility after removal of the device. It has no adverse metabolic effects, especially in obese women, on serum lipids, carbohydrates, liver enzymes, coagulation parameters, blood pressure or weight gain.

The LNG-IUD also protects against ectopic pregnancy and pelvic inflammatory disease, and it increases the body's iron stores by reducing menstrual blood loss. Other non-contraceptive benefits include treatment of symptomatic fibroids, endometriosis, adenomyosis, endometrial hyperplasia, and early-stage endometrial cancer. The prevalence of functional ovarian cysts in LNG-IUD users is approximately 12%. These cysts do not require intervention as they disappear within 4 months of follow-up.

CUSTOMISED GROWTH CHARTS

Prof. J Dornan

There is little logic in expecting all babies to be the same weight at term, and thereafter categorising those that are bigger than expected as macrosomic, and those that are smaller than expected as growth restricted. If we are to improve our ability to determine the size of the fetus at any given gestation, and further to see whether that size is appropriate in that pregnancy, it is essential that the hymn book we are singing from is appropriate for the mother in question. 3.4 kg may well be the average weight of a term baby in our general population, but this weight is what it is, an average. Just as all mothers and fathers are of different sizes, and were themselves of different weights at birth, so their offspring can be expected to follow suit. The future must be, at the first visit, to predict the ideal weight of the baby that each mother should expect. Therefore, introduction of the use of customised growth charts is spreading throughout much of the developed world. This approach has in particular been encouraged by Professor Jason Gardosi, Birmingham. His work and vision will be described.

THE USE OF CARDIAC ECHOCARDIOGRAPHY IN SEVERELY ILL OBSTETRIC PATIENTS

Dr H A Lombaard

University of Pretoria

The place of ultrasound in obstetric practice needs no introduction, but it is usually aimed at evaluating the fetus. In the management of the acutely ill obstetric patient it can be a diagnostic aid. In certain conditions like amniotic fluid embolism and pulmonary embolism, assessment of the right ventricle function and strain and calculating the pulmonary pressure can help to exclude other causes. This is mostly done with trans-oesophageal echocardiography. In cases of acute coronary syndrome echocardiography can help to exclude a diagnosis like pulmonary embolism and by visualising poor ventricle wall movement or abnormal ventricle wall movement a diagnosis of infarction can be made. It can also help in the diagnosis of aorta dissection. If a patient presents in respiratory distress with chest pain, the differential diagnosis would include pulmonary embolism, myocardial infarction, pneumonia and cardiomyopathy. Cardiac ultrasound will be able to make a diagnosis in the last case or indicate normal cardiac function as well as cardiac dysfunction. In cases of severe pre-eclampsia complicated with pulmonary oedema, echocardiography can help to aid the specific pathophysiological pathway and the correct treatment option can be followed. In pregnancy echocardiography cannot replace invasive measurement such as a Swan-Ganz catheter but it can replace a CVP.

In conclusion, echocardiography has a definite place in the management of the acutely ill pregnant patient.

PROGRESS IN ATTAINING THE MILLENNIUM DEVELOPMENT GOALS

Prof. R C Pattinson

University of Pretoria

There are three MDGs that directly affect obstetricians and gynaecologists, namely MDG 4, to reduce infant mortality by two-thirds by 2015 (starting at 1990); MDG 5, to reduce maternal mortality ratio by three-quarters (by 2015); and MDG 6, to reduce the communicable diseases HIV, TB and malaria.

South Africa's progress was reviewed in 2008 with the publication of 'Every Death Counts', and it was pointed out that South Africa was not on track to meet its goals. The major reason for not being on course to meet the goals has been a poor quality of care.

The talk will analyse this and suggest methods that would put South Africa back on track to reach the goals.

EXENTERATION

Prof. Greta Dreyer

University of Pretoria

The aim of this paper is to remind colleagues of what this treatment modality offers and to give an update of its place in modern-day gynaecological oncology. The personal series of the author of the last 5 years will be shared with the audience.

Definition. Pelvic exenteration is a term classically used to describe the so-called ultra-radical procedures needed to remove pelvic malignancies not confined to the central pelvic organs. Initially exenteration always implied the loss of continence, urinary or anal or both, and also implied the loss of vaginal function.

Indications. Because of these losses and the high surgical morbidity inherent in ultra-radical surgery, exenteration will always be limited to a small group of patients with no other treatment options left or who can expect a much better treatment result from exenterative surgery than from other treatments. With the improvements in treatment effect with radiation, chemotherapy and the combination, these treatments, which will potentially spare organs and

organ function, will more often be chosen by the patient.

Today posterior exenterative procedures are offered to patients with recurrent ovarian cancer confined to the recto-vaginal space and pelvis, almost always with retention of anal function. Recurrent central disease after previous radiation also qualifies for exenteration on a few conditions, while some patients with extensive primary disease are also better treated with exenteration. This especially includes patients with soft-tissue malignancies like sarcoma.

Morbidity. The long- and short-term morbidity and the physical and psychological adaptations inherent in these procedures are considerable. Both the patient and the surgeon should be aware of these complications, the morbidity and the risks.

The scarcity of patients and the implications of this surgery imply that few cancer surgeons have the necessary skill, experience and commitment to treat these patients. The selection of patients for this procedure is individualised and depends on the opinion of the evaluating surgeon. Unfortunately only patients evaluated by surgeons supportive of exenteration are likely to be selected.

Disease outcome. It is now well accepted that the survival of patients in whom exenteration was done with curative intent closely resembles that of patients treated with palliation in mind. Both these treatment intentions are therefore acceptable if the patient is well counselled and consents.

SEVERE ENDOMETRIOSIS

Dr A de Bruin

Severe endometriosis involves the ovary, the genito-urinary system, the recto-vaginal space and intestinal endometriosis that involves the small bowel as well as the rectum. This talk will not focus on ovarian endometriosis, but one important factor to remember is that endometriomas are associated with severe disease elsewhere in the pelvis.

Severe endometriosis is not uncommon. Genito-urinary endometriosis includes bladder endometriosis as well as ureteric endometriosis. Bladder endometriosis is relatively rare and represents less than 1% of all endometriosis cases. Partial cystectomy or segmental resection of the bladder is considered the treatment of choice. Ureteric endometriosis is relatively rare and has an incidence of 0.08-1% of patients with endometriosis. A distinction should be made between extrinsic and intrinsic ureteral endometriosis. A higher prevalence of ureteral endometriosis is noted in patients with recto-vaginal nodules >3 cm.

The surgical treatment of endometriotic nodules behind the cervix and in the recto-vaginal septum is aimed at removing the deeply infiltrating fibro-muscular and abnormal glandular tissue in order to relieve pelvic pain, particularly dyspareunia and peri-menstrual dyschezia. The laparoscopic approach is difficult and potentially dangerous. However, attempting this with open surgery is even more difficult as visualisation in the recto-vaginal space is very difficult with open surgery. Of all the types of endometriosis, involvement of the recto-vaginal septum and bowel is the most difficult, takes the longest to operate, and has the most complications and most of the time also the most severe symptoms. It is important to remember that endometriosis, although it can be debilitating, is still a benign disease. It is the aim to achieve as complete removal of disease as possible, but this must also be weighed up against the possible long-term effects of rectal/bowel surgery. Currently the major decision lies between rectal resection and removal of the disease from the rectum without resection. This might include 'skinning' of the disease from the wall of the rectum, or local resection and suturing of the resultant defect.

Operative therapy of endometriosis with intestinal involvement leads to a significant improvement of the symptoms and the patient's quality of life as well as an increased chance of conception. Radical removal of this severe form of endometriosis is possible with current surgical techniques. Advantages of the laparoscopic approach are evident.

The aim is to have complete surgery. This is always the first surgery. This means that there is not a place for incidental surgery for severe endometriosis. These patients should be referred to a unit that has a multidisciplinary team dedicated to severe endometriosis.

SURGERY FOR SEXUAL REASSIGNMENT

Prof. B G Lindeque

University of Pretoria

Patients who suffer from gender dysphoria require psychiatric diagnosis, support and treatment over many years. If this is the only assistance offered the mortality of the disorder is close to 45%, mainly due to suicide. As an international guide the Harry Benjamin Gender Dysphoria Foundation has issued templates for therapy that are widely adhered to. The Sexual Reassignment Clinic at SBAH subscribes to the HBGDF guidelines. After presentation the first years of treatment rest with psychiatrists and psychologists. If living in the desired gender role is successful and the diagnosis is made with confidence the patient is seen at a combined clinic for consideration of hormone treatment. Only if that option is successfully tolerated are patients considered for sexual reassignment surgery.

The most common request is from male to female. As the Act states that a person belongs to a specific gender if that person has the sexual organs of the particular gender, surgery consists of removal of genital organs as first step and then creating functional organs as a second step. In this situation penectomy/orchidectomy is the first procedure performed. In the SBAH clinic the second procedure is a sigmoid colon neovagina procedure. The plastic aspects of creating a functional and aesthetically acceptable vulva are addressed at a third or sometimes fourth procedure. Breast augmentation is not always required due to the effect of the female hormones. If needed this is addressed separately.

For a female to male request the starting surgical procedure should be a total abdominal hysterectomy, bilateral salpingo-oophorectomy and vaginectomy. As the latter is a complex procedure most patients receive the first parts of the procedure separately and quite early in the process. Vaginectomy is then later performed. Creation of a neopenis is quite difficult and belongs to the plastic surgeons. Tissue expansion allows for homograft neopenis

with a central core of silicone. Silicone is also used to fill the neoscrotum created from vulvar skin. There are numerous problems and especially when it is attempted to provide a neourethra for terminal micturition.

In both situations the clitoris or part of the glans penis is retained for sensation.

Regular follow-up is required as complications can occur even at late stages. These include stenosis, lacerations or even fistulation.

THE MANAGEMENT OF GROWTH DISCORDANCE IN TWIN PREGNANCIES

Dr H A Lombaard

University of Pretoria

Selective intrauterine growth discordance (sIUGR) is defined as a difference of 25% in the estimated fetal weight between the two fetuses. sIUGR without twin-to-twin transfusion syndrome (TTTS) complicates between 7% and 14% of monochorionic diamniotic pregnancies with a mortality of 9 to 11% [1]. The causes cannot be explained by genetic discordance but rather by the degree of placental sharing, the quality of implantation, the angioarchitecture and placental transport [2,3]. It also appears that early-onset and late-onset sIUGR have different placental characteristics [4].

To predict patients at risk of developing complications like TTTS, sIUGR and intrauterine fetal death, several screening strategies have been studied. Discordance in NT of more than 20% has been found to identify 55% of cases with a positive predictive value of 34% [5]. A combined system of first-trimester screening to look at discordant amniotic fluid or a CRL difference of more than 12 mm predicts a probability of 79% for a complicated outcome with a 50% survival [6]. At the 16 weeks assessment a discordant amniotic fluid volume and a discordant cord insertion or an abdominal circumference difference (ΔAC) of more than 6 mm and discordant amniotic fluid volume and concordant cord insertion or an ΔAC >13 mm and discordant cord insertion but equal amniotic fluid volume or an ΔAC >24 mm and equal placental insertions and amniotic fluid volumes has a 73% chance of a complicated outcome. If the two are combined 48% of sIUGR will be picked up [6]. The management of these pregnancies is based on detailed evaluation at 11 - 13 weeks 6 days, 16, 20 and 26 weeks to evaluate umbilical artery Doppler, ductus venosus and middle cerebral artery Doppler and in cases of severe discordance and risk of fetal loss selective termination using cod occlusion or laser coagulation [1]. Timing of delivery is based on the presence of complications but from two published studies there is no evidence of benefit for delivery of uncomplicated cases at 32 weeks as long as regular follow up is continued [1].

1. Lewi L, Jani J, Blickstein I, *et al*. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort. *Am J Obstet Gynecol* 2008; 199: 514.e1-514.e8.

2. Lewi L, Van Schoubroeck D, Gratacós E, *et al*. Monochorionic diamniotic twins: complications and management options. *Curr Opin Obstet Gynecol* 2003; 15: 177-194.

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6. Lewi L, Lewi P, Diemert A, *et al*. The role of ultrasound examination in the first trimester and at 16 weeks' gestation to predict fetal complications in monochorionic diamniotic twin pregnancies. *Am J Obstet Gynecol* 2008; 199: 493.e1-493.e7.

ULTRASOUND IN LOW-RISK PREGNANCY

Prof. J Dornan

Given the opportunity and investigative tools, contemporary obstetricians rarely mistime their interventions in high-risk pregnancies in the third trimester. A combination of biophysical, real-time and Doppler ultrasound provides much important information on fetal life. Yet in most developed and many underdeveloped countries, unexplained or unexpected stillbirths occurring in apparently low-risk pregnancies now dominate perinatal mortality statistics.

Cochrane still tells us that there is no place for routine ultrasound in low-risk pregnancy. Is Cochrane telling the whole truth? Should we be doing more to address this question? Logic suggests that the tools we use in monitoring high-risk pregnancy should be transferable to low-risk pregnancy.

Are the problems of the high number of unexplained stillbirths, most of which are associated with IUGR, just to be accepted, or should they be addressed methodically in a prospective randomised controlled trial?

RECURRENT MISCARRIAGE

Prof. J S Bagratee

University of KwaZulu-Natal

Recurrent miscarriage (RM), the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive. The pathophysiology of pregnancy loss is poorly understood and a cause may be found in only about 50% of couples. It is a source of emotional distress to couples. They are prepared to undergo empiric and alternative treatments, even when evidence of success and safety data are lacking. Maternal age and previous number of miscarriages are independent risk factors for a further miscarriage. Between 25% and 30% of women with three successive losses experience a miscarriage in their next pregnancy. However, 70% of couples with idiopathic RM may have a live birth in a subsequent pregnancy without any treatment.

A comprehensive and complete approach to the evaluation of couples with RM should be adopted. The evaluation should include the identification of chromosomal anomalies, uterine anomalies, cervical incompetence, endocrine disorders, thrombophilias and alloimmune anomalies.

Various medical interventions have been used to improve the live birth rate in RM. Traditionally, this has been based on anecdotal evidence, personal bias and the results of small uncontrolled trials. Meta analyses and Cochrane Systematic Reviews have given perspective regarding various treatments in couples with RM.

HOW WILL THE HIV PROBLEM BE CONTAINED IN SOUTH AFRICA?

Prof. Anton Stoltz

Infectious Diseases Unit, FPD and University of Pretoria

South Africa is currently experiencing a health crisis, with one of the worst HIV/AIDS epidemic in the world. Every day more than 1 000 AIDS patients die due to various

opportunistic and co-morbid diseases that drain resources from an already overburdened health service.[1] It is thought that almost half of all deaths in South Africa, and up to 71% of deaths of people between 14 and 49, are directly or indirectly caused by AIDS.[2] New HIV infections are currently as high as 1 500 per day.[3]

Factors such as legislation and systems of government, technology and innovation, economic factors, human activity and social pressures are some of the major factors that are driving this pandemic. Solutions lie in addressing these drivers and to change them around to prevent disease pathways to increase disease sources. But as long as our idols, heroes and leaders are setting an example of polygamy and promiscuity, prevention of HIV infection in the youth is almost impossible to achieve.

Treatment of HIV is at a point where the infection is seen as a chronic disease and life can be extended almost 40 years. This implies that we are constantly increasing the load of people living with HIV in South Africa. Managing this increasing burden of HIV individuals will have to be planned carefully so that treatment interruption is minimised, preventing HIV resistance and no effective treatment.

1. UNAIDS 2008 Report on the global AIDS epidemic

2. Centre for Actuarial Research, South African Medical Research Council and Actuarial Society of South Africa (2006, November), 'The Demographic Impact of HIV/AIDS in South Africa - National and Provincial Indicators for 2006'.

3. News 24.com, 14/03/2007, 1500 new HIV infection daily.

ARV ROLL-OUT IN PREGNANCY: NEW DEVELOPMENTS IN ANTIRETROVIRAL TREATMENT

Dr T M Rossouw

Clinical Head, ARV Clinic, TDH

The ARV treatment spectrum has changed dramatically since the introduction of the first antiretroviral – AZT – in 1986. This presentation will look at current local and international recommendations for the use of ARVs in pregnancy and discuss issues around efficacy, safety and resistance during and after pregnancy. It will then focus on new developments in current drug classes – namely nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PI) – and explore new drug classes, their mode of action, stage of development and possible application of these classes to clinical practice. Classes that will be covered are entry inhibitors, fusion inhibitors, integrase inhibitors and maturation inhibitors.

THE TERRIBLE TRIPLETS: HIV, TB AND MALARIA IN PREGNANCY!

Dr H L Chauke

University of Pretoria

Just as economic meltdown is threatening the very fibre of which the world exists, the same can be said of the strain that HIV, malaria and TB are putting on the health sector, especially in the developing world. When these conditions manifest in pregnancy, the diagnosis is often difficult and management challenging. The effects on the fetus need to be taken into consideration. Where HIV and one of the other two conditions co-exist in a pregnant woman, the challenges become enormous. An attempt will be made to offer some practical advice on how to approach the three conditions in pregnancy.

CONTRACEPTION FOR OLDER WOMEN

Prof. J Guillebaud

Given that FSHs are unreliable for diagnosis of complete loss of ovarian function, contraception may cease:

• **After age 50**, after stopping any hormones: waiting for the 'officially approved' one year of amenorrhoea.

• This is the obvious plan for deciding when to discontinue **copper IUDs**, **condoms**, or **sponges** and **spermicides** (which latter are adequate during this time of drastically reduced if not absent fertility)

But what to do if the woman uses one of the hormonal methods or HRT, which mask the menopause?

• If on DMPA, Nur-Isterate or COC (or Evra patch or vaginal ring where available) – age above 50/51 is the time to switch to something else. Reason: these hormonal methods are needlessly strong contraceptively, and the known risks though rare increase with age. But what to use instead?

• The POP, or an implant, or the LNG-IUS (Mirena), or a sponge/spermicide with or without ongoing HRT: these contraceptives will add minimal or negligible medical risks that do not increase with age – even to age 60! So it would be risk-wise acceptable simply to switch to or continue with these contraceptives (duration of the HRT is a separate issue) till the latest age of potential fertility has been reached, then just stop the contraception. (NB again, no FSH or other tests!) When is that latest fertile age?

• A good guess is age 55 – the Faculty of FP, in their Guidance document, quote Treloar's evidence that 95.9% have by then ceased menstruation for ever. Moreover it is highly probable that in the other 4.1% any cycles they have above 55 will not be fertile.

• This appears an acceptably safe policy despite Guinness Book of Records reporting one or two older mothers above 55.

• As a safeguard, all are advised to report back if a period does in fact happen after ceasing their method, in which case added use of POP, sponge or spermicide might be wisest for some further months.

Another option for older users of COC or of injectables, IF:

- they have passed 50, *and*, after a trial of discontinuation using barriers or spermicides, they have:
- vasomotor symptoms (can usefully ask COC-users if they already noted flushes, at end of each pill-free interval responding to first few of next pills) *and*
- two separate high FSH levels one month apart (confirmatory in this specific case) *and*
- the amenorrhoea continues beyond this trial period (reporting back if it doesn't).

With due warnings of lack of certainty, these women may cease all contraception earlier than the approved one year post age 50.

Finally, what are the actual and expected advantages of giving HRT by LNG-IUS plus oestrogen by any route (NB in which case changing this is advised every 4 years in UK)?

• Contraceptive HRT

• No-period, usually no-bleed HRT – before proof of ovarian failure

• No heavy/painful loss HRT, nor other menstrual symptoms

• Minimal systemic progestogen HRT: ? might ? be better for breast cancer risk (as progestogens also affect this).

Plus still giving the expected quality-of-life benefits of HRT.

HORMONE THERAPY AFTER WHI

Dr P Swart

It would seem that the initial confusion that followed immediately after the publication of the WHI has now largely been thought through, analysed and some sort of consensus agreed upon. However, there still remain large areas about the management of the menopause that need to be studied. These are questions that were not intended to be studied by the WHI and will need populations different from the WHI population with different endpoints to be studied. These include questions such as the effect of dosage, age, route of administration and the effects of concomitant disease.

There is very little if any discrepancy in the conclusions of the prospectively performed RCT WHI trial and the observational studies such as the Nurses Health Study as far as osteoporosis, thromboembolism, breast cancer and colon cancer are concerned. There were however significant differences in the conclusions concerning strokes, cardiovascular events and dementia.

This could probably be explained by the inherent differences in the characteristics of the study populations such as age, BMI, smoking, concomitant aspirin use and flushing. Calculating the weight attributed to these different parameters still needs to be done.

It would seem that the age at initiation of HT is crucial as far as the effect on coronary heart disease and dementia is concerned. Initiation soon after the menopause probably renders protection against these outcomes. Starting HT in elderly patients remote from the final menstrual period however increases the risk of these events, particularly where there are other risk factors such as early dementia or hypertension.

The mechanisms for these differences and data to support these conclusions will be presented. The effects of HT where there is more consensus will also be presented.

BLADDER HYPERACTIVITY: EVERYTHING STILL ISQ?

Dr Z Abdool

Bladder hyperactivity or overactive bladder (OAB) is the most common bladder problem in later life, affecting up to 100 million people worldwide. It is a chronic medical condition with a huge economic and psychosocial impact. OAB has evolved as a syndrome and has become more rigorously researched and somewhat better understood by experts. Recently it has been suggested that 'urgency' is the driving factor in all other symptoms of OAB including frequency, nocturia and urge urinary incontinence. Despite a standardised definition of urgency the term has created both clinical and intellectual confusion. Apart from surgery, bladder retraining and pharmacological intervention remains the mainstay of treatment. Current and future trends in the management of OAB will be discussed.

FERTILITY-PRESERVING SURGERY IN CERVICAL CANCER

Dr D Oram

With the introduction of computerised call and recall cervical cancer screening in 1988 in the UK, there has been a dramatic reduction in the incidence of invasive disease. However, the success of the screening programme has produced a relative increase in asymptomatic, screen-detected early-stage disease in young women. This, together with the fact that many women are postponing starting a family, has led to an increased consideration of fertility-sparing surgery in these cases.

Radical vaginal trachelectomy was first performed at Bart's in 1994 following Daniel Dargent's seminal publication. The results of this 15-year series will be presented, including selection criteria, patient counselling, and pre-operative assessment. The surgical technique will be illustrated and the outcome data associated with the procedure will be discussed. Two outcome measures are relevant: first the effectiveness of the technique in curing the cancer; and secondly, because the justification for the procedure is dependent on an overwhelming desire on the part of the patient to preserve her fertility, pregnancy rates and outcomes will also be presented.

Finally, the refinement of the surgical technique and the aspirations for future developments will be addressed, which it is hoped will provide a suitably controversial platform for audience participation and discussion.

DEVELOPMENTS IN REVERSIBLE MALE CONTRACEPTION

Prof. J Guillebaud

At long last a systemic male contraceptive appears on the horizon, perhaps – though one hesitates to say it after so many false dawns – even within the next 10 years. The most promising approaches are:

1. A long-acting testosterone ester by injection or implant, coupled with an injectable or more probably implanted progestogen.

2. The pharmacological semen-blocking method, or 'dry orgasm' pill.

1. The first approach is one of **suppressing spermatogenesis** by pituitary inhibition (similar to the effect of the COC in women) but maintaining masculinity and libido through the androgen component. But it has proved difficult to get the right dosing balance in all men, so as to provide efficacy through azoospermia, or sufficiently marked oligospermia, plus normal masculinity; and yet avoid unwanted hyperandrogenic manifestations such as

acne, aggression, prostatic hypertrophy or increasing the already-present male susceptibility to arterial disease. So, currently, this approach is no longer being actively pursued.

2. The **'dry orgasm' pill** is a novel non-hormonal approach based on the same highly unusual side-effect of two drugs with quite different main actions, first reported many decades ago. As far back as 1961, American psychiatrists were reporting the side-effect of a phenothiazine, succinctly put in the title of a 1968 case report: 'Thioridazine-induced inhibition of masturbatory ejaculation in an adolescent'.

Later – acting on reports going back even further to the mid 1950s – workers in Israel published [Homonnai *et al., Contraception* 1984; 29: 479-491] a pilot study in 13 men of the identical strange effect of an alpha-adrenergic blocker, under the title 'Phenoxybenzamine – an effective male contraceptive pill'. This title was not perhaps an overstatement, since at no time while on treatment with 10 - 30 mg of the drug did any of the volunteers produce any semen at all at ejaculation: yet there was apparently complete restoration of semen volume and quality on discontinuation. There was no evidence of retrograde ejaculation or of effects on testosterone, FSH, LH or prolactin. Of greatest interest is that none of the men reported any adverse effects on libido, erection, sexual performance or on their sensations of orgasm and ejaculation – despite no fluid emission.

Where has this interesting possibility got to, in the 25 years since that pilot study? The original drugs had too many reported side-effects, indeed thioridazine is no longer in the British National Formulary and phenoxybenzamine has a very restricted use as a hypotensive in the treatment of phaeochromocytoma. But the pharmacologists Amobi and Smith at King's College Hospital have continued working systematically on our excised vasectomy specimens from the Margaret Pyke (London) and Elliot-Smith (Oxford) clinics, and have identified the mechanism of action (on the vas and also, necessarily to result in dry ejaculations, 'downstream' from the prostate). The original drugs, some new ones they have identified and also tailored ones that have been synthesised with the same 'chemical signature', all if given at the right (low) dosage contrive to paralyse the longitudinal muscles of the Wolffian duct system while still permitting the circular muscles to contract. This leads to loss of the usual co-ordinated ejaculatory 'Mexican wave'; instead there is a sphincter action, reversibly preventing emission of both sperm and seminal fluid.

At the time of writing funding is being sought to take the most promising candidate drugs forward through all the required preliminary phases of clinical testing for efficacy and safety. This will certainly cost millions of dollars and take at least 10 more years – 60 years since those first reports.

Administration issues. Many women have the serious concern that they would have difficulty in trusting a man who *said* he was using any form of 'male pill' – or even if he truly was, that the average male would be a safe and conscientious user, given he has much less personal 'investment' in contraception?

Both the above approaches have advantages here:

• the first is likely to be an implant, and as this is likely to be in the upper arm like Implanon a user's sexual partner can confirm for herself its presence and likely ongoing action, by simple palpation!

• the 'dry orgasm' method also has the potential to be a slow-release implant. But additionally it could be marketed as 'pre-coital' pill – if as seems probable it would work at full efficacy about 2 - 4 hours after being swallowed. This also could help to reassure the anxious wife or partner, since she could supervise him taking the tablet at supper-time, in readiness for action at bed-time!

WHO'S WHO IN THE LABOUR WARD

Prof. J Dornan

Labour wards throughout the world bear a certain physical resemblance to each other.

They also all have their share of high emotion, and that is just among the staff! However, in many, increasingly there is a power struggle over ownership of the mother. Obstetricians, midwives, doulas, partners, husbands, mothers, paediatricians, anaesthetists, are all feeling that they deserve more attention. Indeed professional positioning is in danger of becoming more important than the welfare of the mother and her offspring.

It is now time for accoucheurs to regroup and place the mother at the centre. This will require the clock to be turned back, and forward, at the same time. The labour ward should not be an amphitheatre in which there are special interest groups vying for supremacy. Rather it should be an area where all disciplines work together for the common good of the mother and her baby. The essence is teamwork, with the mother and her baby REALLY the key personnel involved.