REFLECTIONS

The gynaecological subspecialties: Advances in women's health

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Under Professor Dennis Davey's leadership, the Department of Obstetrics and Gynaecology recognised the need for subspecialist expertise and training. Thus, the gynaecological subspecialties were developed, the first of which was gynaecological oncology. We review the research, and subsequent clinical application, which has evolved from the subspecialist units.

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Reproductive medicine

The clinical services in reproductive medicine were among the first of their kind in South Africa (SA). In the mid-1970s a medical endocrinologist was appointed to develop gynaecological endocrinology and a service laboratory was established in collaboration with the Departments of Chemical Pathology and Medicine to support the clinical input. In 2006 a Reproductive Medicine Unit was established, comprising the gynaecological endocrine clinic and laboratory, infertility services, menopause care, an endocrine antenatal clinic, a recurrent miscarriage clinic, family-planning services and attendant subspecialist surgery. We discuss the resulting clinical research in contraception and interception, the polycystic ovary syndrome and infertility in Africa.

Contraception and interception

Fertility regulation has always been an interest. In 1995 the UK Medical Research Council and the UK Department for International Development (DFID) jointly funded a programme of research within the Contraceptive Development Network (CDN) for developing new contraceptive methods in a network of centres in Cape Town, Edinburgh, Shanghai, Hong Kong, and later Sagamu, Nigeria. Initially, surveys accessed the opinions of contraceptive users about potential new methods. Subsequently, we studied the potential of hormonal male contraception and non-oestrogen-containing female contraception.[1-6]

Our contraceptive research unfortunately demonstrates that the knowledge of both healthcare providers and users is often inadequate. A survey of educational programmes is under way; one aim is to understand why the intra-uterine device (IUD) is under-utilised and patients and healthcare providers have limited knowledge of this method.[7] These studies contribute to our services and we hope to see considerable improvement in the next decade.

Benign gynaecological disorders

Our unit has focused on polycystic ovary syndrome (PCOS). We have a database comprised of the details of almost 1 500 women who presented with PCOS to our clinical services; information includes metabolic and endocrinological profiles currently being prepared for publication.

Family studies have demonstrated a higher prevalence of PCOS in the sisters (45.4%) and daughters (55.6%) of women with PCOS compared with the general population. An adverse lipid profile was also found in mothers and sisters of probands with PCOS.

We are collaborating with the University of Oxford on the genetics of women with benign gynaecological disorders, including PCOS and uterine fibroids. As a result, two publications reviewing possible genetic mutations in women with uterine fibroids have been produced. This research has considerable significance, given the high prevalence of uterine fibroids in African women. It is interesting that the genetic mutations of our patient population are similar to those of Europe, despite the higher prevalence and earlier presentation in Africa.[8]

Infertility

We have explored infertility in Africa from the angle of the psychological and social experience of infertility, and the inter-relationship of this experience with infertility-related healthcare. Qualitative research found that infertility was a highly distressing and often stigmatising experience for women.[9] For many, the experience of involuntary childlessness was shaped by emotional distress, marital instability with fear of divorce or infidelity, ridicule from members of the family and community, verbal and, at times, physical abuse from the partner, and considerable social pressure to have a child. In contrast, some women felt well supported by their husbands and social network, and appeared to cope better with their inability to conceive.

Our research and publications from other African countries show that women carry the main burden of infertility, but men too are affected. Men frequently experienced sadness, pain and feelings of emptiness, and some expressed anger and frustration.[10] The distress described by women and men in qualitative studies proves quantifiable.[11] Comparison with studies using the same research instrument suggested a greater width and depth of distress among infertile women in SA compared with infertile women in western industrialised countries.[12] Similarly, male partners of infertile

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couples in our community had higher levels of distress on all subscales compared with male partners of pregnant women;[13] therefore infertility profoundly influences the lives of SA women and men and is frequently associated with distressing psychological and social consequences.

This reality of infertility is shaped by the generally high value placed on children in African countries. Qualitative social science research from sub-Saharan Africa describes these roles in rich detail: children complete marriage, confer social status, protect rights of property and inheritance, assist with labour, satisfy emotional needs, offer social security in old age, and provide continuity by maintaining family lineage. Closely linked to the value of children are the motives for men and women to desire parenthood. Infertile couples attending Groote Schuur Hospital (GSH) endorsed most motives of the Parenthood-Motivation-List, an instrument developed to measure parenthood motives.[14] In Western industrialised countries, men and women desired children predominantly for personal happiness and fulfilment, and the conjugal relationship;[15] therefore, it appears that in addition to happiness and parenthood, other factors from culture, society, continuity and heritage influence the desire to have children in our setting.

The burden of disease has become an increasingly important topic in health science research and resource allocation in the past 2 decades. Existing generic instruments are not sensitive to infertility, especially in African and other developing countries where people's lives are often profoundly affected and disease-specific instruments are, by and large, lacking. To address this challenge our unit is developing instruments to contribute to our understanding of the needs of women with infertility.

Gynaecological oncology

The Gynaecology Oncology Unit was one of the first subspecialties established and is an important source of research. Over the past 15 years it has focused on cervical cancer prevention in low-resource settings. The Khayelitsha cervical cancer screening project (KCCSP) was established in 1995. Cervical cancer is now relatively rare in women living in developed countries, where secondary prevention using the Pap smear, combined with colposcopy and the removal of precancerous lesions, has been very successful. In contrast, no low-resource country has managed to initiate or sustain cervical cancer prevention strategies, due to a lack of resources. Our project evaluated alternative protocols for cervical cancer prevention, specifically to evaluate different screening tests compared to cytology, and to measure the impact on the reduction in cervical cancer precursors.

In each of the initial 2 projects, just under 3 000 previously unscreened women aged 35 - 65 years were screened with 4 screening tests: *(i)* cytology; *(ii)* screening for high-risk types of human papillomavirus (HPV) (DNA testing); *(iii)* visual inspection with (5%) acetic acid (VIA) to visualise aceto-whitening, an indication of an underlying cervical cancer precursor; and *(iv)* cervicography, in which the cervix was photographed after VIA using a specially adapted camera. Women with abnormal tests were referred for colposcopy and histological assessment in phase 1. In phase 2, a random sample of women with negative results for all 4 tests was referred for colposcopy to eliminate verification bias.

Cervicography had low sensitivity and specificity; it was considered of value for VIA quality control but not as a primary screening test. Data indicated that screening with VIA and HPV DNA testing could identify 1 in 4 or 1 in 5 screen-positive women, necessitating either referral or treatment.[16] Data also indicated that both VIA and HPV DNA testing could lead to considerable overtreatment of screen-positive women. To interrogate whether that mattered, we established a randomised controlled trial to evaluate screening safety, acceptability and efficacy. A total of 6 555 women aged 35 - 65 years were randomised to 1 of 3 groups: *(i)* treatment if HPV-positive (treatment was performed by primary care nurses at primary care level using cryotherapy to ablate the transformation zone of the cervix – a procedure performed on site without the need for local anaesthetic), *(ii)* treatment if VIA-positive, or *(iii)* delayed treatment for 6 months, regardless of the screening test result.

This study showed that HPV DNA testing combined with cryotherapy resulted in a 75% reduction in cervical cancer precursors compared with the control/delayed treatment group. However, VIA was associated with only a one-third reduction in cervical cancer. Evaluated longitudinally, the performance of VIA, compared to HPV DNA testing, was significantly inferior over a 36-month period of follow-up.[17,18]

This work has been duplicated in several developing countries on the Indian sub-continent, and in Latin America and Africa. While HPV DNA testing is superior to VIA, there is no test that allows point-of-care testing and treatment, or HPV test that is affordable, although several are in development. Linking screening to treatment in one visit is desirable to overcome the many logistical barriers women in poor countries must overcome to access healthcare. While inferior, VIA allows a screening infrastructure to be created in low-resource settings, which in turn will be available once improved quality tests are developed.

While secondary prevention of cervical cancer through screening has dominated prevention efforts in the last century, primary prevention with vaccines against high-risk HPV (aetiologically associated with cervical cancer) is highly effective in preventing HPV-related disease. Available vaccines include the bivalent vaccine (against HPV 16, 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and quadrivalent vaccine (against HPV 6, 11, 16, 18; Gardasil, Merck and Co., Inc, West Point, Pennsylvania, USA). The KCCSP has completed a randomised double blinded phase 1/11 trial of the safety and immunogenicity of the bivalent vaccine in HIV-positive women aged 18 - 25 years. The first such trial in the world, it has shown that the vaccine is as safe and immunogenic as it is in HIV-negative women.

The project is recruiting women to an HPV therapeutic vaccine trial. The vaccine, developed by Inovio, is designed to promote regression of dysplastic lesions caused by infection of the cervix with HPV types 16 and 18. This novel approach would allow circumvention of the complex processes required by secondary prevention with screening tests.

Urogynaecology

Urogynaecology focuses on managing women with pelvic floor dysfunction. In treatment, the boundaries between the specialties are blurred and input is often required from gynaecology, urology and colorectal surgery. A progressive step in treating women with urinary incontinence was the establishment of the multi-disciplinary female continence clinic at GSH. This clinic, with equal input from gynaecology, urology and physiotherapy was one of the first of its kind in SA. It is an ideal platform for research into female urinary incontinence, focusing mainly on developing innovative management strategies.

The overactive bladder (OAB) is an additional area of interest, with a prevalence of 15 - 20% in the general population. Standard management of OAB includes anticholinergic drug therapy, bladder retraining and pelvic floor muscle exercises. A significant proportion of women have a suboptimal response to treatment; an Australian study showed that after 10 years of attending a specialist

incontinence clinic, only 30% of women showed improvement.[19] A small retrospective study of 100 patients attending our clinic over the past 12 years showed similar results; 62% of the women claimed that their condition was unimproved or worse. This has prompted research into novel treatment strategies in women with OAB in our department over the past 15 years.

In Europe and the USA, treatment with sacral nerve stimulation, by implantation of a neuromodulator in the region of the sacral nerve roots, demonstrated remarkable improvements in urinary urgency and incontinence. As this device is costly and requires an infrastructure for insertion and technical support, there was an unmet need for a simplified device. We studied a simplified nerve stimulator implanted in the abdominal wall, with a neuromodulating effect via the pudendal nerve. This device was associated with significant improvements in women with refractory urinary incontinence.[20]

A randomised controlled trial in the USA by Emmons *et al.*[21] demonstrated significant improvements in continence outcomes in women treated with bladder-specific acupuncture compared with relaxation-point acupuncture. This prompted us to investigate acupuncture for treating urge urinary incontinence. Our prospective cohort study on women with refractory OAB demonstrated significant improvement in quality-of-life scores following bladder-specific acupuncture.[22] Unfortunately, it is difficult to ascertain the extent of the placebo effect with acupuncture trials; despite this, we believe that it is an inexpensive and safe treatment alternative in these women.

Stress incontinence surgery has evolved rapidly over the past decade with the development of minimally invasive slings inserted under the mid-urethra; this has replaced major surgical interventions such as the colposuspension. The next-generation device, the mini-sling, requires a single 1 cm vaginal incision; this can be done as an outpatient procedure under local anaesthesia. Our department has published a meta-analysis of these devices, and found a lack of good level-one evidence on their efficacy.[23] In collaboration with the University of Stellenbosch, we are undertaking a randomised controlled trial comparing the Needleless single incision sling to the standard transoburator tape.

Our unit also has a keen interest in maternal injuries sustained at childbirth. We performed a case control study comparing the outcomes of third and fourth degree perineal tears in HIV-positive and -negative women. HIV-positive women had poorer functional faecal continence outcomes,[24] suggesting that HIV may have an impact on anal sphincter muscle function. A larger clinical study is required to substantiate our findings and a laboratory-based study on the impact of HIV on muscle function may reveal interesting data.

Conclusion

The development of a strong subspecialty programme in gynaecology has improved the care of women accessing our services. The resultant research has contributed to changes in therapeutic approaches and service delivery and should ultimately impact on the heavy burden of disease caused by reproductive ill-health among women.

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