

Report from a study visit to London, UK, in January-February 2012.

Kresten R. Petersen, Senior Consultant, Ph.D., Department of Obstetrics and Gynaecology, Odense University Hospital, Denmark.

Thanks to an educational leave from my department and a grant from the NFOG foundation, I had the opportunity to spend 4 weeks in London in order to update myself within the field of gynecological endocrinology and paediatric and adolescent gynecology.

The period consisted of

- 1). Visit to Prof. Nicholas Panay studying premature menopause and premenstrual syndrome.
- 2). Participation in "Training Day and Advances in Paediatric and Adolescent Gynaecology" arranged by the Royal College of Obstetricians and Gynaecologist, and British Society for Paediatric and Adolescent Gynaecology.
- 3). Visit to Dr. Sarah Creighton studying paediatric and adolescent gynaecology

Ad 1).

Prof. Panay is the Head of the tertiary referral center "West London Center for Menopause and Premenstrual Syndrome" with clinics at the Queen Charlotte's Hospital and Chelsea and Westminster Hospital. In addition he is the Chairman of the British Menopause Society and Editor in Chief of Climacteric.

The women with premature ovarian failure (or dysfunction which may be a more proper term in cases where the ovaries have not been removed) referred to the clinics tend to be properly diagnosed from the referring institutions, but the records are thoroughly revised and supplementary tests and examinations are performed when necessary. Simultaneously their previous treatment – if any – is revised, in order to secure a replacement of the hormones that normally should be produced at this age. This concept of replacement or substitution of deprived natural hormones is emphasized to the women who may be influenced by the media-induced concepts of the presumed deleterious effects of exogenous hormones in general.

The aim of the replacement is to come as close to the physiological levels of hormones as possible. The treatment is individualized according to the choice of the women, her medical records and the possible need of contraception, recognizing that women with premature ovarian dysfunction may have occasional ovulations.

The preferred substitution is transcutaneous estrogen with addition of micronized progesterone in a sequential or continuous manner depending on the woman's wish for bleeding. Alternatively the progestogen may be administered through a progestogen-releasing IUD or the women can have transcutaneous progestogen along with the estrogen. Oral preparations may be used if the women may wish so, but is not recommended as a first line treatment.

At present, combined oral contraceptives are not first choice as natural hormones are preferred, but OCs can be considered in selected women for contraceptive reasons.

The ovarian failure also reduces the androgen production which may be a problem especially in the women with surgically induced menopause. If tiredness and low sexual desire is predominant, testosterone substitution is often helpful in these women. The treatment is usually given transdermally but may be given as subcutaneous deposits in long term treatment. The effects of testosterone substitution on vascular function and selected metabolic variables are currently studied in the unit.

The knowledge of premature ovarian failure (or dysfunction) is scarce and recognizing that long term randomized studies will be difficult to perform in this group of women, a database has been established, presently including 450 women from the West London area. It is hoped that this database can be expanded to other parts of Great Britain and provide further information on this disorder and also form the basis of future research.

Apart from women with premature menopause women with naturally occurring menopause is also seen in the clinic. These women will typically be "problematic" as conventional hormone therapy has proven to be ineffective or because of current or past medical conditions. In the former group their previous therapy is reviewed and adjusted preferably using transdermal administration of estrogen in combination with transdermal or intrauterine progestogen. Transdermal or subcutaneous testosterone may be recommended in women where depression of mood or decreased libido is a problem.

If estrogens are inappropriate or contraindicated, the climacteric symptoms may be treated with clonidine, SSRI's or gabapentine. The effect of blockage of the stellate ganglion in resistant cases of hot flushes is currently evaluated in a controlled trial.

Women with severe premenstrual symptoms (PMS) are also referred to the clinic. These women have commonly been resistant to first line therapy elsewhere and have symptoms which may have led to breakdown of interpersonal relationships and to an interference with normal activities - including work. The previous medical records and treatments (including the widespread use of herbal medication, vitamins and minerals) are carefully reviewed and additional tests may be performed in order to exclude other medical conditions.

When such conditions are excluded the primary aim of the treatment is to suppress the cyclic secretion of ovarian hormones which is considered the primary cause of the condition. The choice of treatment is made according to the preferences of the women and in women reluctant to hormone therapy SSRI's may be an appropriate alternative. These preparations have proven to be effective in PMS and randomized studies have shown that luteal phase administration is as effective as continuous intake, which may make the treatment more acceptable to some women, as it can be regarded as different from the treatment used for psychiatric disorders.

When using hormonal suppression of ovarian function, the combined oral contraceptives preferable with progestogens of low androgenicity is one of the first-line options and continuous or extended intake is recommended. Likewise have transdermal estrogen with cyclic progestogen administration proven to be

effective, but this treatment does not secure contraception, and intrauterine progestogen administration is often preferred. This will also reduce the progestogen load in these women who frequently show a pronounced sensitivity to the side effects of progestogens.

In women resistant to the above treatments GnRH analogues have proven to be effective to relieve the symptoms. This treatment should not be given for more than 6 months without estrogen substitution preferable as continuous combined therapy. In women where this treatment has been effective and tolerable, oophorectomy may be considered as the ultimate means of ovarian suppression. In such (rare) cases hysterectomy is often recommended in order to avoid the need for progestogen protection of the endometrium.

The RCOG guideline for PMS has been written by Prof. Panay and can be found via www.pms.org.uk or www.rcog.org.uk

The visit to the department was very inspiring and rewarding due to the academic approach to the clinical and therapeutic problems associated with menopause and PMS. It also provided new insights and perspectives to the various treatment options for these women. I was received with great hospitality by Nick Panay and his colleagues, and I was impressed by their willingness and efforts to share and discuss their knowledge and concepts.

Ad 2.

Participation in "Training Day and Advances in Paediatric and Adolescent Gynaecology" arranged by RCOG and British Society for Paediatric and Adolescent Gynaecology, arranged by Dr. Pallavi Latthe, Birmingham and Miss Sarah Creighton, London (Programme: http://www.sigia.it/files/londra_23_24.pdf)

The course is held annually and took place at the Royal College of Obstetricians and Gynaecologists, London. The first day has a more general approach to the gynaecological problems associated with adolescence, while day two covers more specialized subjects.

Day one included a number of instructive up-to-date lectures on chronic pelvic pain, bleeding disorders and dysmenorrhoea, PCOS, contraception and sexually transmitted diseases. The lectures provided an excellent overview over problems frequently encountered in common gynaecological practice and gave some valuable practical hints on how to handle the problem specific to adolescents.

On day two the morning sessions covered Disorders of Sex Development with special reference to Rokitansky syndrome including the diagnostic, therapeutic and supportive aspects of these rare conditions (1 to 4-5000 births). In line with the ACOG guidelines, it was recommended that dilatation should be the first-line treatment for vaginal aplasia. Dilatation achieves sexual function in approx. 80% and surgery should be reserved for the few remaining cases. The choice of the correct surgical procedure among the myriads available is a matter of debate. "The inventiveness of the gynaecological surgeons is infinite. The ideal procedure has yet to be found" as it was stated. In the UK the laparoscopic vaginal stretching procedure

(Vechiatti) seems to be the one preferred at present, but was stressed that vaginal dilatation should be an integrated part of the postoperative management. .

The psychological support of the patient and her family was addressed in a separate lecture, stressing the profound impact on personality and family structure of the diagnosis of disordered sex development. It was strongly recommended that diagnosis and treatment of these disorders should not take place without the integration of professional, psychological support.

A special session was reserved for a free communication competition where a number of interesting research projects were presented, and in a very interesting session some of the gender-issues linked to the upcoming Olympics in London was discussed..

At these meetings a special person who has been working within the field of paediatric and adolescent gynaecology is invited to give a memorial lecture in honor of Sir Jack Dewhurst, one of the leading figures of gynaecology and obstetrics in the last century. This year, our NFOG colleague professor Dan Apter from Finland was invited to give this lecture in recognition of his longstanding clinical, educational and scientific efforts to promote contraception and reproductive health in Finland as well as internationally. Dan gave an excellent lecture on the ups and downs (most ups!) of sexual education in Finland and its impact on society through the last decades.

The course gave an excellent introduction to some of the gynaecological problems associated with adolescents ranging from issues of general interest (bleeding disturbances, contraception, STI) to more rare disorders of disturbed sexual development. The course was well-organized and is warmly recommended.

Ad 3.

Miss Sarah Creighton is head of Paediatric and Adolescent Gynaecology at the University College London Hospitals(UCLH) located on Euston Road in Central London. She is Board Member of the British Society of Paediatric and Adolescent Gynaecology and is a key person in the international scientific and educational activities of adolescent gynaecology and disorders of sexual development.

The department sees female patients with complex disorders of sex development including genital malformations, androgen insensitivity syndromes and adrenal hyperplasia from the greater part of London and South East England. The patients may have additional malformations and are treated in close cooperation with paediatric endocrinologists, urologists and general surgeons from UCLH and from the Children's Hospital in Great Ormond Street.

The clinic has an integrated psychological service for these patients with special trained psychologists and councilors, who assisted the girls and their family in the initial and subsequent coping with the consequences of these disorders. This included also the prospects for future fertility which – depending of the development of uterine transplantation - may be adoption or surrogacy.

The clinic includes a number of nurse-specialists who have special training in the counseling and care for these patients including pre- and postoperative measures e.g. vaginal dilatation.

The principles for the treatment of these patients are briefly described in the following section.

Rokitansky Syndrome.

These girls are born without a uterus (or may have hypoplastic uterine remnants) and have a very short or absent vagina. Their ovaries and external genitalia are normal and they have a normal female genotype. The diagnosis is usually made when the girl is examined for primary amenorrhea.

Vaginal dilatation is the primary treatment in order to obtain the possibility of vaginal intercourse. The treatment is started after individual evaluation of the patient – often at about the age of 16. The girls are instructed by a nurse-specialist, who they can contact during the treatment and at any time they may need it afterwards. The programme includes the application of dilators for 20-min a day often for 3 months or more. This treatment is successful in about 80-90 % of the cases, but should be followed afterwards with dilatation once or twice a week, if they don't engage in regular intercourse.

If dilatation fails, the surgical procedure of choice is the laparoscopic Vecchietti procedure. Here, the vagina is stretched by applying continuous traction on the vaginal bud by sutures introduced through the top of the vagina to the abdominal wall using a special stretching device placed on the abdomen.

Androgen insensitivity Syndromes (AIS).

Girls with androgen insensitivity syndromes (karyotype 46 XY, syn. Testicular feminization, Morris Syndrome) are typically referred to the clinic after the diagnosis is made when ruling out primary amenorrhea or when an undescended testis is found in a presumed inguinal hernia in a girl. These girls have normal external genitalia, a short (or virtually absent) vagina and no uterus or tubes.

Because of increased risk of malignant transformation in AIS, removal of the gonads is traditionally recommended at the time of diagnosis. However, there seems to be growing evidence that the risk of malignancies in these cases may be equal to the one found in boys with retained (2-4%) testes. Surgery is therefore preferable postponed to the age of 16-17 y as the peripheral conversion of the testosterone produced in the gonads to estrogens seems to secure a more smooth development of puberty than the one induced by exogenous hormones, which has to be given for pubertal inductions when the gonads are removed at an earlier stage. Estrogen substitution is started immediately after gonadectomy as individuals with AIS seem to be even more exposed to osteoporosis than women with premature ovarian failure.

In patients with a short or absent vagina, the procedure follows the principals described for the Rokitansky syndrome

Patients with Swyers syndrome (46,XY, syn. XY gonadal dysgenesis) have normal external genitalia but in contrast to girls with AIS they have a vagina and an uterus, probably due to lack of Mullerian Inhibitory Factor produced in the normal fetal testis. No sex hormones are produced in the dysgenic gonads of these patients. Malignant transformation is more common in these patients (approx. 30%) and removal of the

gonads is recommended at diagnosis, followed by estrogen (and progestogen) substitution after induction of puberty has been completed.

Congenital adrenal hyperplasia.

Girls with androgenizing congenital adrenal hyperplasia due to hydroxylase deficiencies diagnosed as newborns are usually seen in the clinic close to the expected time of puberty in order to evaluate if problems with menstruation can be anticipated. The girls are then examined under general anesthesia and it is also evaluated if the result of previous surgery, performed in order to correct concomitant urological or gasto-intestinal malformations may interfere with sexual or reproductive function. The exam is performed with a paediatric urologist or general surgeon and aims at planning additional surgery, which is performed at a later stage after thorough discussion with the patient and her parents.

Reconstructive procedures in order to secure sexual and reproductive function is usually not done at this stage, but is considered when the girls are about 17-18 y. depending of their maturity and preferences. These procedures may vary from simple vaginal repair to complex procedures involving vaginal reconstruction in cases with a high fusion of the vagina and urethra.

The substitution of adrenal hormones is performed by paediatric endocrinologists and there is a close corporation with dermatologists in cases with pronounced hirsutism.

In addition to these well defined disorders a number of patients with various "minor" abnormalities of the Mullarian system are seen in the clinic. These include women with vaginal or uterine septae and bicorn uteri of varying severity. In general, these uterine abnormalities are treated only if there are complications i.e recurrent miscarriages or obstructed outflow from a uterine horn.

The visit to Miss Creighton was very instructive and it was a great opportunity for me to see such a "concentration" of these rare cases in a setting where such an experience was gathered. I was impressed by the integrated and empathic approach to these patients. The focus was not only directed at the surgical and endocrine aspects but much attention given to the psychological and social aspects of the patients as well.

I was very well received by Dr. Creighton and her colleagues and I enjoyed very much our discussions on the rare as well as the more common aspects of our specialty.

