GENDER-SPECIFIC MEDICINE
THE NEW PROFILE OF GYNECOLOGY

Originalarbeit:

Gruber DM, Huber JC. Gender-specific medicine: the new profile of gynecology.
Gynecol Endocrinol 13:1-6; 1999

Univ.Prof. Dr. Doris Maria Gruber

Universitätsklinik für Frauenheilkunde
Abteilung für Gynäkologische Endokrinologie und Reproduktionsmedizin
Währinger Gürtel 18 –20
A-1090 Wien
email: ordination@frauenaerztin-gruber.at
www.frauenaerztin-gruber.at

Ordination
Wiedner Hauptstraße 95/6
A-1050 Wien
Mo und Do 16 h-19 h
Tel: 01 – 544 92 02

ABSTRACT

The science of gynecology is undergoing a change and is swiftly turning into a holistic discipline, i.e. that of gender specific medicine. The rationale for this is that the hormones of the ovary are not only responsible for reproduction but also perform a number of extragenital functions that extend far into other disciplines, giving rise to a different frequency of diseases in women than in men. For example, females are five times more likely to be affected by rheumatoid arthritis than males, the same also holding true for autoaggressive conditions. This phenomenon may be accounted for by the fact that physiologic autoaggression is involved in the reproductive process. Similarly, there is a difference between women and men in regard to the sicca phenomenon, or to such disorders as connective tissue weakness, cellulite, venous conditions or hyperyholesterolemia. A cause-related treatment of such problems is now available through a specific endocrine therapy. That is why gynecologists in future will increasingly have to adopt an interdisciplinary approach.

One hundred years ago Professor Wertheim, the famous surgeon in gynecology, performed his first radical operation on a patient with carcinoma of the cervix.

In contrast to abdominal radical hysterectomy, Schauta preferred the vaginal axis and promoted the vaginal radical hysterectomy. Two surgical traditions have emerged from this scientific discussion, and for most of the last century, surgery has been one of the main topics in gynecology. There has also been a common opinion in our discipline: The qualification and value of a gynecologist was exclusively measured by the number of hysterectomies and abdominal operations, which he performed.

But time has changed and, following the rapid progression and research in the field of gynecological endocrinology, the profile of our discipline is also changing. The priority of surgical intervention in gynecology is declining and the new qualification for gynecologists will be measured by their capacity to prevent many surgical interventions and to treat the various gender-specific disorders in the light of the scientific background of gynecological endocrinology. What we have learned in the past few years is that there is a strong influence of ovarian steroids on neurological, dermatological, rheumatological and metabolic diseases, and that gynecology will therefore also change its traditional name, giving rise to a new discipline: *gender - specific medicine*.
To strengthen this development it is necessary to focus on characteristic different gender-specific problems which will help to illustrate the facts.

- Gender-specific *DEPRESSION*

As we know from epidemiological investigations, the prescription rate of psychopharmacological drugs rises dramatically in the female in the perimenopausal period. The explanation for this increase in the prescription rate cannot only lie in the phsychosomatic lability and other phenomena occurring at that time in a woman´s life. It is not only the so-called empty-nest syndrome which can cause psychovegetative dysfunctioning. Indeed, there is an endocrinological disposition, and one of the major physiological explanations for a gender-specific depression can be found on the level of the gamma- aminobutric acid (GABA) receptor. The ubiquitous receptor for gamma-aminobutric acid in the central nervous system is also occupied and stimulated by progesterone. Progesterone exerts the same effect as barbiturates like benzodiacepam (Study). In occupying the GABA receptor, progesterone is also capable of opening the chloride canal, thereby inducing an anxiolytic and sedative effect. The receptor itself consists of different sub-units, with each sub-unit changing beween several isoforms (Sighart). This leads to a strong fluctuation, depending on the time of the menstrual cycle. A dependency on individual stress situations can also be observed which may result in different GABAergic reactions. The influence of progesterone on the GABA receptor can be measured by standardized procedures, using hippocampal cells (Twyman).

Interestingly, and this would be a new aspect in hormone replacement therapy (HRT), it is not only the hormone that is replaced which shows a biological effect, but some metabolites also induce their own biological action; therefore, the way of metabolisation in HRT will become more important for our understanding of the effects and side-effects of different exogenously applied hormones. It is known that norethisterone has no amplification effect on the GABA receptor. This finding may explain the clinical phenomenon, that some patients taking progestagens are predominantly complaining about depression and psychovegetative problems. We therefore believe that gender-specific depression may also be a progesterone-deficiency symptom. Natural progesterone stimulates the GABA receptor in cases of progesterone insufficiency when the anxiolytic effect of GABA is not supported by the luteal phase hormone – progesterone - and this is why depression and psychovegetative disorders occur.

The role of progesterone in other GAGA-dependent diseases such as for example, in unilateral focal epilepsia, was demonstrated and published (Herzog 83).

But it is also in cases of premenstrual depression (Herzog 86), and migraine, that progesterone exerts its beneficial effect through the occupation of the GABA receptor. As a therapeutical procedure, we use natural progesterone intravaginally to avoid hepatic metabolisation.

But progesterone does not only seem to become a psychotropic drug. It was introduced as a neurotropic agent years ago by Baulieu (Jung-Testas), who demonstrated that progesterone may enhance myelin formation. This important finding may have a major impact on many other neurological diseases in the future.

- Gender-specific *AUTO-IMMUNEREACTIONS*

Although the idea that hormones affect immune responses has been around since the late 19th century, researchers are only now beginning to closely scrutinize the cyclic nature of the female immune system. The basic observation that a woman´s immune responses are stronger than those of men has been confirmed by a host of studies. While a woman´s estrogens keep her immune response "up", a man´s androgens tend to suppress his immune system. The male system is also subject to little variation after puberty, while the female system spikes up at puberty, is depressed during pregnancy, then returns to its previous level after pregnancy, and is lowered again after the onset of menopause (Morell). While a women may be less susceptible to infections, she is far more likely to contract an autoimmune disease, such as systemic lupus erythematosus, multiple sclerosis, or rheumatoid arthritis. The strong influence of hormones on a woman´s immune system helps to explain why women are more susceptible to autoimmune disease. As an illustration of this point , women with lupus have increased levels of estradiol, which in turn leads to increased levels of circulating antibodies. Very few men suffer from lupus, presumably because of the protective effects of testosterone, which keeps the male immune system humming at a steady, if lower, level (Casson). Very often autoimmune diseases run in families. For example, a mother may have lupus while her daughter has rheumatoid arthritis.

Chronic autoimmune thyreoiditis is another example for a gender-specific disease. There is a 1:10 ratio between male and female patients. A similar ratio can be observed in rheumatoid arthritis. Therefore, the medical delegation on the conference in Peking called for more scientific immunological research in and for female patients.

The different immunological reactions beween men and women can be partly explained and understood in the light of the reproductive potential of the female organism. During a normal menstrual cycle, when no pregnancy was achieved, the corpus luteum gets destroyed (Tabibzadeh). The functional procedure of luteolysis is not that of a simple mechanical destruction; instead, a highly sophisticated immunological process starts: Some cell compounds from the luteal organ are removed from antigen presenting cells, which will offer these particles to T-lymphocytes as antigens. This is why an antigen-antibody reaction begins and the corpus luteum is destroyed within 24 hours in an autoimmune reaction. This is the same biological reaction as can be observed in other cases of autoimmune disorders and autoaggressive reactions. Yet there is another interesting point: FSH stimulates antigen presentation but LH suppresses this reaction, an aspect which might be of importance for reproductive medicine in the future.

In contrast to autoaggressive disorders, but in a similar way as in some phathophysiological aspects, there is the so-called arthopathia climacterica. This disorder occurs mainly during the menopause and manifestsitself with pain in the minor finger joints (Metka). Arthralgia is also a gender-specific problem which can be found predominantly in female patients. The etiological factor is the cessation of

ovarial hormone production. As a decline of estradiol also occurs in cases of amenorrhea and post delivery, symptoms of arthralgia can also be observed during these periods. As a successful treatment, topical estradiol can be offered to these patients. Estradiol is able to penetrate the skin and thus may relieve joint pain.

The pathophysiological background can be found on the biochemical level of the cytokines. As it is well known, estradiol suppresses the nuclear faktor kappa B (NFκB), an ubiquitous inflammatory messenger, which is normally inactivated by its inhibitor, I-kappa B (IκB) (Bart v Burg). Estradiol does not only suppress the NFκB, but also enhances the production of IκB and thus reduces the inflammatory reactions, which are then mediated by interleukin-6 (IL-6). NFκB is a transcriptional factor, occupying the promotor of IL-6 and thereby stimulating gene expression. This mechanism is important in cases of estradiol deficiency and constitutes the genesis for osteoporosis and perhaps even for neurodegeneration.

The fluctuation of sexual steroids in the female body, a mechanism which is unknown in the male organism, is responsible for a different expression or suppression of catabolic transmitters. This might be part of the reason why females suffer far more from autoaggressive disorders than their male counterparts.

- Gender-specific *SICCA SYNDROME*

The sicca phenomeneon is predominantly found in females. The clinical characteristics can be limited to the eyes, but symptoms can also be observed in the vagina, in the oropharyngeal region and on the entire skin. The occurrence of the sicca phenomenon is linked to an estrogen deficiency and is observed mainly during the menopause. The ocular symptoms can easily be treated by topical application of estradiol. Eydrops consisting of 0.005% estradiol can remove the disorder known as conjunctivitis sicca in many cases. (Sator 98). This therapeutical procedure is also successful in patients suffering from glaucoma (Sator96, 98).

Dryness of the vagina and urogenital problems are very common symptoms in the menopause and can easily be treated by local estrogen application or by systemic HRT (FANTL).
Dryness of the entire skin is a symptom afflicting many menopausal women. Using the effect of systemic HRT or topically applied estrogen on aging facial skin is the proper treatment (Brincat,Creidi).
A very recently published paper on premature skin aging focuses on the connection between UV light and skin damage, its influence on collagen synthesis and degradation and on ways of influencing it (Fisher). It is especially the dermal collagen that UV light has deleterious effects on. There are the matrix-metalloproteinases (MMP), a family of proteolytic enzymes specifically degrading collagen. MMPs are the only enzymes known to carry out the initial attack on the helico-collagen under physiological conditions: They are stored in lysosomes in the

form of an inactive enzyme (pro-collagenase) and are continuously secreted into the extracellular matrix. They are activated by endogenous pro-collagenase-activators such as stromelysin. Several metalloproteinase inhibitors known as tissue inhibitors of metalloproteinases (TIMP) control the activity of MMPs (Simon). Interestingly the activity of MMPs can be suppressed by progesterone (Bart v Burg). That is why progesterone will gain much interest as a substance against skin aging.

- Gender-specific *ADIPOSITY*

There is also some evidence that the development and maintenance of adiposity are gender-specific problems (Wang, Aloia, Kirchengast 1997). Estradiol, progesterone and androgens all have different effects on the fat tissue in various regions of the female body. In abdominal fat cells, testosterone induces lipolysis, whereas in the gluteal femoral area, lipid accumulation in adipocytes is enhanced by estradiol and progesterone (Björntorp, XU)
Body composition changes throughout the lifespan and sexual steroids seem to have an important influence on fat and muscle distribution (Borkan, Ley, Longcope, Kirchengast Homo).
The selective accumulation of body fat in different regions depends on the balance between the inflow and outflow of free fatty acids from the adipocytes .
Progesterone and estradiol enhance lipoprotein lipase activity in the gluteal femoral area of the female body and amplify the incorporation of free fatty acids (Rebuffe, Eckel). Androgens have a strong influence on body composition; however their anabolic effect has been overemphasised in the past. Recent studies demonstrate that lipolysis is enhanced by testosterone. Androgens stimulate the expression of the β3-adrenergic receptors on the surface of the adipocytes. This is an important step towards lipolysis and free fatty acid mobilisation (Marin, Lovejoy). In times of androgen deficiency, the triglycerides inside the adipocytes cannot be mobilized, and the lipoytic process is stopped. Androgen deficency can often be observed in menopausal women and becomes clinically manifest with abdominal adiposity. This problem can be partially solved by androgen substitution (Haarbo). This type of fat accumulation often goes together with a loss of libido. In a placebo controlled study we investigated the lipolytic effect of topically applied androgen on abdominal adiposity, measuring the fat tissue by using a DEXA technique. We were able to demonstrate that there was a significant fat-mobilizing effect of the non-aromatizing androgen that was applied on the upper body region (Gruber).

CONCLUSION

It has been demanded by a variety of societal groups for quite some time now that gynecologists should be more than specialists for genital matters. Instead, they should offer holistic advice and assistance to women in regard to all problems that are gender-specific and due to the different hormonal regulation of the female body.

The female endocrine system is involved in a number of body compartments, a fact which explains the gender-specific nature of many disorders. This is why the discipline of gynecology will be called upon to increase not only its diagnostic, but also its therapeutic range of services in an interdisciplinary manner.

References

Twyman RE, Mc Donald RL. Neurosteroid regulation of GABA (A) receptor single-channel kinetic properties of mouse spinal cord neurons in cultutes. *J Physiol* 1992;456:215-45

Sieghart W. Stucture and pharmacology of γ-aminobutyric acid-A receptor subtypes. *Pharmacol Rev* 1995; 47:181-234

Study RE, Barker JE. Diazepam and (-) pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of γ-aminobutyric acid responses in cultured central neurons. *Proc Natl Acad Sci* 1981;78:7180-4

Herzog AG, Deibel MM, Schomer D, Vaitukaitis JL, Gschwind N. Temporal lobe epilepsy: an extrahypothalamic pathogenesis for polycystic ovarian syndrome? *Neurology* 1983; 88 (Suppl 2) S189

Herzog AG. Intermittant progesterone therapy and frequency of complex partial seizure in women with menstrual disorders. *Neurology* 1986;36:1067-70

Jung-Testas I, Schumacher M, Robel B, Baulieu EE. Demonstration of progesterone receptors in rat Schwann cells. *J Steroid Biochem Mol Biol* 1996;58:77-82

Morell V. Zeroing in how hormone affect the immune system. *Science* 1995; 269: 773- 5

Casson PR, Andersen RN, Herrod HG, et al. Oral dehydroandrosterone in physiologic doses modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 1993;169:1535-9

Hurtley S, Bendit J. Women´s Health Research, A Special Report. *Science* 1995;269:765-801

Tabibzadeh S. The signals and molecular pathways involved in human menstruation, a unique process of tissue destruction and remodelling. *Mol. Hum. Reprod* 1996;2:77-92

Metka M, Heytmanek G, Enzelsberger H, Schurz B, Kurz C. Der Gelenkschmerz in der Prä- und Postmenopause. Arthropathia climakterica. *Geburtsh u Frauenheilk* 1988;48:232-4

Bart van der Burg, Paul T. van der Saag. Nuclear factor-kappa-B/steroid hormone receptor interactions as a functional basis of anti-inflammatory action of steroids in reproductive organs. *Molec Hum Reprod* 1996;2:433-8

Fantl JA, Cardozo L, McClish DK, and the Hormones and Urogenital Therapy Committee. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the hormones and urogenital therapy committee. *Obstet Gynecol* 1994;83:12-8

Sator MO., Joura EA, Golaszewski T, Gruber D, Frigo P, Metka M, Hommer A, Huber JC. Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol. *Brit J Obst Gynecol* 1998;105:100-2

Sator MO, Gruber DM, Joura EA. Hormonal influence on intraocular pressure. *Lancet* 1996; 348:761-2.

Sator MO, Akramian J, Joura EA, Nessmann A, Wedrich A, Gruber D, Metka M, Huber JC. Reduction of intraocular pressure in a glaucoma patient under hormone replacement therapy. in press *Maturitas* 1998

Brincat M, Versi E, Moniz CF, et al. Skin collagen changes in postmenopausal women receiving two different regimen oestrogen therapy. *Obstet Gynecol* 1987;70:123-7

Bincat M Moniz CF, Studd JWW. et al. Sex hormones and skin collagen content in postmenopausal women. *BMJ* 1983;187:1337-8

Creidi P, Faivre B, Agache P, Richard E, Haudiquet V, Sauvanet JP. Effect of conjugated oestrogen (Premarin) cream on ageing facial skin. A comparative study with a placebo cream. *Maturitas* 1994;19:211-23

Fisher GJ, Wang ZQ, Datta SD, Varani J, Kang S, Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* 1997;337:1419-28

Simon C, Gimeno MJ, Mercader A, et al. Cytokines-adhaesion molecules - invasive proteinases. The missing paracrine/autocrine link in embryonic implantation. *Molec Hum Reprod* 1996;2:405-2

Wang Q, Hassager C, Ravn P, Wang S, Christiansen C. Total and regional body-composition changes in early postmenopausal women: age-related or menopause-related? *Am J Clin Nutr* 1994;60:843-8

Aloia JF, Vaswani A, Russo L, Sheehan M, Flaster E. The influence of menopause and hormonal replacement therapy on body cell mass and body fat mass. *Am J Obstet Gynecol* 1995;172:896-900

Kirchengast S, Gruber D, Sator M, Hartmann B, Knogler W, Huber J. Menopause-associated changes in female fat patterning estimated by dual-energy X-ray absorptiometry. *Annals Hum Biol* 1997;24:45-54
Xu X, De Pergola G, Björntorp P: The effects of androgens on the regulation of lipolysis in adipose precursor cells. *Endocrinology* 1990;126:1229-34

Björntorp P. Metabolic Implications of Body Fat Distribution. *Diabetes Care* 1991;14:1132-43

Borkan GA, Hults DE, Gerzof SG, Robbins AH, Silbert CK. Age changes in body composition revealed by computer tomography. *J Gerontol* 1983;38:673-7

Ley CJ, Lee B, Stevenson JC. Sex and menopause - associated changes in body fat distribution. *Am J Clin Nutr* 1992;55:950-4

Longcope C. Androgen and estrogen conversion ratios in aging women. *Maturitas* 1979;2:13-7

Kirchengast S, Gruber D, Sator M , Knogler W, Huber J. The fat distribution index - a new possibibility to quantify sex typ specific fat patterning in females. *Homo* 1997;48:285-93

Rebuffe´-Scrive M., Basdevant A., Guy-Grand B. Effect of local application of progesterone on human adipose tissue lipoprotein lipase. *Horm Metabol Res* 1983;15:566

Eckel R.H. Lipoprotein Lipase - a multifunctional enzyme relevant to common metabolic diseases. *N Engl J Med* 1989;320:1060-8

Marin P, Holmang S, Jonsson L, Sjostrom L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obesity* 1992;16:991-7

Lovejoy JC, Bray GA, Bourgeois MO, Macchiavelli R, Rood JC, Greeson C and Partington C. Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women- a clinical research center study. *J Clin Endocrinol Metab* 1996;81:2198-203

Haarbo J, Marslew U, Gotfredsen A, Christiansen C. Postmenopausal hormone replacement therapy prevents central distributionof body fat after menopause. *Metabolism* 1991;40:1323-6

Gruber DM, Michael O. Sator, Sylvia Kirchengast, Elmar A. Joura, Johannes C. Huber. Effect of percutaneous androgen replacement therapy on body composition and body weight in postmenopausal women. Maturitas 29:253-259;1998