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SYMPOSIUM OF SCIENTIFIC TRAINING OF THE POLISH SOCIETY OF ANDROLOGY – 21ST DAY OF ANDROLOGY

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Report

On October 25–26, 2019, the 21st Andrological Day organized by the Polish Society of Andrology (PTA) was held at the Borowiecki Hotel in Lodz. The organizational part of this event was taken by the Foundation for the Medical University of Lodz (FUMED) in cooperation with the Organizing Committee and the Scientific Committee chaired by prof. Jolanta Słowikowska-Hilczner.

On October 24, the meeting was preceded by a clinical andrology test exam, organized for the third time by PTA. 15 doctors participated in it, 12 of them obtained a positive result and received a PTA Certificate in clinical andrology. The scientific part of the Conference began with a greeting from the PTA President prof. Jolanta Słowikowska-Hilczner and the presentation of the PTA Youth Award named by prof. Michał Bokinić, which in 2018 was received by PhD Kamil Gill from Szczecin. The laureate presented the winning study in a short presentation.

In scientific sessions lectures were given by foreign guests: prof. Ewa Rajpert-De Meyts from Denmark, prof. Davor Jezek from Croatia, prof. Aleksander Giwercman and prof. Yvonne Lundberg-Giwercman, prof. Gerhard

Van der Horst and prof. Stefan Du Plessis from South Africa, prof. Valentinas Matulevicius and prof. Birute Žilajtiene from Lithuania. In addition, many excellent lecturers from Poland gave lectures. Topics concerned issues related to male fertility, the impact of endocrine disorders on male reproductive function, the possibilities of urological therapies in erectile dysfunction and many others. Diagnostic methods and therapeutic options in infertility were also discussed. Representatives of basic science presented the results of the latest research related to the physiology and pathology of the male reproductive system. The session of short scientific presentations was also very popular.

The General Meeting of Members of the Polish Society of Andrology was held during the Conference. A new Executive Board and Audit Committee of PTA were elected. MD PhD Szymon Bakalczuk from Lublin became the new PTA President. The meeting ended with thanks to the lecturers, participants, organizers and sponsors of the Conference and an invitation to the Conference in 2020, which will take place in Warsaw.

Abstracts of lectures

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GUIDELINES FOR CARE IN TRANSEXUALISM

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Determining prevalence in transsexual population is problematic. It is recognized that among adult men it is 0,005–0,014%, while among women – 0,002–0,003% (DSM-5, 5th edition, 2018). Recently, we have statistics indicating that there may be more people describing themselves as transsexual, transgender, or gender-non-conforming. The reasons for differences should probably be wider understanding of the problem today. We can observe more people reporting gender dysphoria since it was decided to move away from treating transgenderism in terms of psychopathology. Such people feel discomfort and suffering not only because of the mismatch of body to how they feel, but also when they cannot express their identity. Not everyone wants to change the appearance, for some it is enough to be able to function in felt sex. For years we have had a discussion around the model of care in transsexualism. Both already existing American DSM-5 classification and the pending international ICD-11 classification, exclude gender dysphoria from the category of personality and behavioral disorders. This raises questions about whether and how to treat a condition that is not considered a disorder. According to The World Professional Association for Transgender Health (WPATH), transgenderism is a matter of diversity, rather a variant of sexuality than a pathology. The issue of gender identity disorders in children is still a problem. It raises questions about how much you can interfere with the natural maturation process. WPATH periodically presents a comprehensive and detailed document regulating standards of conduct towards transgender people. In 2017, recommendations on medical treatment in transsexualism were jointly published by European and American endocrinological and andrological associations. A position regarding social, health and legal situation of transgender persons was presented by Polish Sexological Society. In Poland, the model for dealing with such cases is criticized, but remains unchanged.

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DIABETES, ADVANCED GLYCATED END PRODUCTS AND MALE INFERTILITY

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Diabetes mellitus (DM) is an embodiment of various metabolic pathologies and represents one of the most substantial contemporary health hazards. Currently more than 420 million people have diabetes and it is projected that 10.4% of the global population will be affected by it in 2040.

Studies have shown that DM affects male reproductive function. Some of the reported effects include a decrease in sperm motility, alteration in sperm kinematic properties, increased abnormal sperm morphology, decreased seminiferous tubule diameter, increased spermatogenic disruption and decreased number of Leydig and Sertoli cells.

The origin of male sterility have been explored at tissue, cellular and molecular levels. However, probing on the cause of male fertility impairment from the dimension of bio-macromolecules and protein composition is minimal. The exposure of proteins, amino acids and lipids to the carbonyl group of reducing sugars eventually leads to the formation of pathological levels of advanced glycation end products (AGEs) under metabolic conditions such as DM. AGEs acts by independently producing reactive oxygen species (ROS) or by binding to their receptors (RAGE) and have been implicated in various pathologies. There are limited and fragmented information on the impact and role of AGEs in the male reproductive tract.

This paper will aim to review the existing literature with regards to AGEs and their implication for male fertility. It will furthermore focus on recent findings from a diabetic animal model by highlighting the interplay between DM, AGE, RAGE and mitogen-activated protein kinase signalling in the testis of diabetic rats, which can result in altered sperm function and may further contribute to male infertility.

Eliza Filipiak

INFLUENCE OF HPV INJECTION ON SEMEN QUALITY AND MALE FERTILITY

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Human papilloma virus (HPV) are agents of the most common sexually transmitted diseases. More than 150 types of HPV have been identified so far, among them several is classified as *high-risk HPV* (hsHPV) and this group is known to be responsible for development of malignancies (eg. cervical, vulvar, vaginal, anal, penile cancer). Emerging evidence indicates that HPV in semen has a negative influence on semen quality and male fertility. Seminal HPV is present in about over a dozen percent of male patients appointed for fertility problems (Laprise et al.: Hum Reprod. 2014, 29, 640–651). HPV is associated with decreased sperm concentration, motility and increased chromatin fragmentation index

(Jeršovienė et al., *Medicina* (Kaunas). 2019, 55 (7), 377) (Boeri et al., *Hum Reprod*. 2019, 32 (2), 209–217). Regarding reproductive success, it was shown that intra-uterine insemination (IUI) with HPV-positive semen is less effective and that above a ratio of 0.66 HPV virions/spermatozoon no pregnancies occurred (Depuydt et al.: *Fertil Steril*. 2019, 111 (6), 1135–1144). Garolla et al. (*Fertil Steril*. 2016, 105 (1), 65–72) also have shown that assisted reproduction techniques (IUI and ICSI) are less effective when HPV-positive semen is used as well as that the miscarriages rate is higher in this group. As proved in above mentioned studies, but also in other scientific papers, HPV localization in semen (on sperm vs on exfoliated cells) is essential for reproductive success – localization on sperm means poorer prognosis. Spermatozoon with HPV (virus localizes in equatorial region of sperm head) has the ability to fertilize the egg (however it can be impaired) but HPV negatively influences embryo development and early pregnancy stages (Foresta i wsp.: *PLoS One*. 2011, 6 (3), 1–9). Other interesting study revealed that anti-HPV vaccination of male partners resulted in increase in spontaneous pregnancies rate and live births in vaccinated group (Garolla i wsp.: *Sci Rep*. 2018, 17, 8 (1), 912). Siristatidis et al. (*Ultrasound Obstet Gynecol*. 2018, 51 (1), 87–93) performed meta-analysis concluding with caution that presence of HPV infection in the male partner seems to exert a negative effect on reproductive success.

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EXTERNAL QUALITY CONTROL OF SEMEN ANALYSIS PROGRAM SPERMCONTROL – RESULTS AND COMMENTS FOR THE ROUND NO. 1

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SpermControl – A Program for External Quality Control of Semen Analysis (www.spermcontrol.pl) was founded in 2019 as the first Polish national program for quality assurance of semen analysis. SpermControl is based on WHO 2010 recommendations (WHO laboratory manual for the examination and processing of human semen). During Round 1, 44 participants from Poland participated and submitted results (starting from June 2019). Among the participants, 36% work in general diagnostic labs, 25% in specialized semen labs or scientific labs and 39% in infertility clinics. Four parameters

were assessed: 1) concentration (preserved sample sent by courier); 2) progressive and general motility (video); 3) vitality (video, eosin stain); 4) morphology (shipped Diff-quick stained slides). Two samples were analyzed for each parameter.

The greatest uniformity was observed for progressive motility (median and standard deviation: 45.5 ±6.2 for Sample 1 and 48 ±7.5 for Sample 2). The most problematic parameter was concentration: several outliers were observed among results (median, standard deviation and min./max.: 11.1 ±19.3, 7.9–128.1 for Sample 1 and 25.4 ±31.3, 7.8–217 for Sample 2). Morphology was found to lie within the range 1–16 (median = 5, IQR = 2) for Sample 1 and 0–8 (median = 1, IQR = 2) for Sample 2.

Most participants received results comparable with the median value and with expert results, indicating that the standard of semen analysis was high. In some cases, however, the results were far from the 95th percentile, used as the reference value.

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PARTICIPATION OF GENITAL HEAT STRESS IN THE ETHIOLOGY OF SPERM PARAMETER DISORDERS

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It is well known that for effective sperm production, the male gonads require the stable thermal environment at a minimum of 2°C below the body core. A prolonged exposure of the scrotum sack to elevated temperature leads to disturbances in the thermoregulatory mechanisms and, as a consequence, results in the phenomenon of testicular overheating. This can be responsible for a reduction of semen quality due to the partial or complete blockade of spermatogenesis. In this context, the exposure of the testes to elevated temperature is considered to be a risk factor for male infertility. The participation

of thermogenic factor in the etiology of sperm parameter disorders is frequently observed in heterogeneous clinical pathologies such as cryptorchidism and varicocele. The negative impact of local hyperthermia on the fertilizing potential of spermatozoa may be related to the reduction of conventional seminological parameters such as sperm concentration, motility and/or morphology, and the magnitude of these disorders probably depends on the severity of this factor. It is suggested that defects in male gametes initiated by a thermogenic factor can result from its harmful effect not only on spermatogenesis but also on sperm maturation in epididymis. The main possible pathways involved in the development of male infertility in individuals exposed to local hyperthermia include oxidative stress and apoptosis. Markers of these processes can provide additional nonconventional semen parameters potentially useful in assessing the fertility status of men exposed to genital heat stress.

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HOW CAN ANDROLOGY IMPROVE RESULTS OF INFERTILITY TREATMENT?

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Assisted reproductive technology (ART) – *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) represent today the cornerstone of infertility treatment. There is an increasing focus on optimizing the methods of ART with less and less attention given to attempts of developing non-invasive medical treatment modalities.

The management of infertility is mainly focusing on the female partner with less attention paid to the options offered by involving andrological expertise. However, there is now increasing evidence that more extended andrological involvement may add to improving the results of ART, reduce the burden of heavy hormonal treatment given to the female partner as well as, possibly, contribute to the improved health of ART-children.

A new, potentially interesting concept of treating male subfertility is use of follicle stimulating hormone (FSH) in selected males with oligoasthenoteratozoospermia. A number of studies have demonstrated that FSH treatment increases the chance of gravidity – *in vivo* and *in vitro*, thereby reducing the need of and improving the results of ART.

Another important aspect is testing for sperm DNA strand breaks. Several studies have shown that sperm DNA fragmentation index (DFI) may be used for finding the most efficient method of infertility management. Furthermore, it cannot be secluded that ART pregnancies accomplished with spermatozoa having high level of DFI

may represent a hazard for the health of the children. Therefore, attempts should be made to develop pharmacological strategies for reducing DFI and thereby increasing chances of spontaneous pregnancies and reducing the potential risks of ART.

More focus on the male partner of the infertile couple may not only improve the outcomes of infertility treatment but also reduce the treatment burden on the female partner and the risk of male mediated transgenerational toxicity.

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RISK OF PROSTATE CANCER IN MEN UNDERGOING ASSISTED REPRODUCTION

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Register-studies (Giwercman et al.: *Int J Cancer*. 2005, 115 (6), 994–997; Jorgensen et al.: *Cancer*. 2008, 112 (4), 919–923; Ruhayel et al.: *Cancer Causes Control*. 2010, 21(10), 1635–1643) as well as one meta-analysis (Mao et al.: *Sci Rep*. 2016, 6, 19210) have reported lower risk of incident prostate cancer for childless men than biological fathers. Other studies have conversely indicated that men with impaired fertility are at higher risk for prostate cancer than fertile men (Walsh et al. *Cancer*. 2010, 116 (9), 2140–2147; Eisenberg: *J Urol*. 2015, 193 (5), 1596–1601; Rosenblatt et al.: *Am J Epidemiol*. 2001, 153 (12), 1152–1158). Previous studies have been limited by either small numbers of study subjects, self-reported diagnoses, or short follow-up time. Apart from limited power, one of the major obstacles in this type of studies is to define the male part's contribution to the infertility of a couple.

We hypothesized that men having to undergo assisted reproduction, and in particular intracytoplasmic sperm injection (ICSI), would have most hampered fertility compared to men receiving classical *in vitro* fertilization (IVF) or conceiving naturally.

By sourcing data from national registries: The Swedish Medical Birth Register, the Swedish Cancer Registry, and the Swedish Quality Register for Assisted Reproduction, all fathers (n = 2 108 569) and their first child born 1994–2014 (n = 1 181 490) were identified. ICSI fathers were compared to those who had become fathers by natural conception (controls) and IVF fathers regarding incident prostate cancer during a follow up of total 51 990 101 person-years until 2016. Sensitivity analysis stratified upon age at diagnosis of prostate cancer.

The results showed immense risk for early-onset prostate cancer, before 55 years of age, generally considered more aggressive, in men referred for ICSI compared to those conceiving naturally (ICSI HR = 1.86, 95% CI = 1.25

to 2.77, $p = 0.002$; IVF HR = 1.51, 95% CI = 1.09 to 2.08; $p = 0.01$). These men may hence already have a latent tumor at the time of ICSI, why the possible benefits of targeted screening should be considered.

Stawomir Jakima

PHARMACOTHERAPY IN SEXUAL PREFERENCES DISORDERS

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Sexual criminals' therapy is one of the most important ways of prevention of recommitting the crime, which is most notable among the criminals with the preference disorders. In addition to the psychotherapy, pharmacological reduce of sexual impulses and tension, which can be intensified by sexual fantasies and para-filial behaviours, can be used. However pharmacotherapy requires precise diagnostic, laboratory test, examination and control of the side side effects. There are also exact contraindications for using those kind of drugs. Recently antiandrogen medications (Cyproterone acetate, Medroxyprogesterone acetate), GnRH agonists and SSRI are preferred and anxiolytics are recommended ad hoc. (Garcia: Curr Psychiatry Rep. 2013, 15 (5), 356; Holoyda i wsp.: Curr Psychiatry Rep. 2016, 18 (2), 19). However the pharmacotherapy should be just a part of whole therapeutic process and should not be used routinely in every case.

Davor Ježek

NEUROENDOCRINE PROPERTIES OF LEYDIG CELLS

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Leydig cells are situated in the interstitial compartment of the mammalian testis. In human, these cells are responsible for secretion of 96% testosterone/androgens. The ultrastructure of Leydig cells shows typical characteristics of steroid-producing cells. Despite these common features, one can occasionally observe a sort of „atypical” Leydig cells with a large body and central cytoplasmic projection, resembling to the axon. Moreover, at the ultrastructural level, the afore-mentioned cytoplasmic projection is abundant in microtubules and microfilaments similar to those of neurons. The projection ends with a slight synapse-like dilatation containing small vesicles. These vesicles look a lot like synaptic vesicles. Immunohistochemical studies have demonstrated both in the adult and foetal human Leydig cells the expression of neurohormones, neurotransmitters, neuropeptides

and glial cell antigens. The antigens expressed by Leydig cells include neuronal markers, enzymes involved in the synthesis of catecholamines, neuropeptides and their receptors, glial cell antigens, calcium binding proteins and components of the NO/cGMP system. Thus, Leydig cell do not act only as endocrine producers of androgens but also as a part of a diffuse neuroendocrine system. The development of the genital ridge occurs in the close proximity of the development of medulla of the suprarenal gland that is of ectodermal origin. Neural crest cells massively populate the mesenchyme near the genital ridge, thus forming the large provisory medulla of the suprarenal gland. Some of these cells could be diverted inside the genital ridge, transforming themselves into neuroendocrine Leydig cells. Recent findings indicate that Leydig cells precursors inside the genital ridge, pericytes, may be programmed into the neuroendocrine cells. Since Leydig cells can be easily obtained via testicular biopsy and cultivated, one can speculate about their potential therapeutic use in the treatment of neurodegenerative diseases.

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EXPOSURE TO ENVIRONMENTAL PHENOLS AND SEMEN QUALITY.

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During the past decades a possible degradation in human semen quality has been debated intensively and has become an important public health issue. A controversial review article of 61 studies analyzing sperm concentrations in fertile men and in men of unknown fertility published between 1938 and 1990 by Carlsen et al. 1992 (Carlsen et al.: BMJ. 1992, 305, 609–613) showed a significant decrease in sperm concentrations and in semen volume. Although a tendency to decreasing semen quality over time has not been firmly established to date, such a possibility had raised new concerns about man made environmental endocrine disrupting factors such as parabens, triclosan, bisphenol A which might affect human fertility.

The aim of the study was to examine the association between exposure to environmental phenols (triclosan, oxybenzone, bisphenol A) and semen quality: main semen parameters, sperm morphology, sperm chromatin structure and the level of reproductive hormones (FSH, estradiol, testosterone).

The study population consisted of 344 men who were attending an infertility clinic for diagnostic purposes with normal semen concentration of 15–300 M/mL. Participants were interviewed and provided semen, blood, saliva and urine samples. The interview included questions about demographics, socio-economic status,

medical history, lifestyle factors (consumption of alcohol, tobacco, coffee intake, cell phone and sauna usage), and physical activity. Urine samples collected were analyzed for triclosan, bisphenol A, oxybenzone using gas chromatography ion-tap mass spectrometry method.

Urinary concentration of BPA increase the percentage of immature sperm (HDS) ($p = 0.018$), estradiol and testosterone level ($p = 0.02$ and $p = 0.04$ respectively) and decrease motility ($p = 0.03$). Additionally, a positive association between the urinary concentrations of triclosan 50th-75th percentile and ≥ 50 percentile and percentage of sperm with abnormal morphology ($p = 0.016$ and $p = 0.002$, respectively). No association was found between exposure to oxybenzone and any examined semen quality parameters and the level of reproductive hormones.

The results of the study are important as this is the first such study in Poland assessing the level of environmental exposure to parabens, triclosan and oxybenzone and their impact on semen quality.

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DEPRESSIVE MOOD DISORDERS IN MEN RELATED TO THE BIRTH OF A CHILD

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Although the term *postpartum depression* is primarily associated with women's experience, the growing interest in the mental health of men who have become fathers indicates that men can also suffer from it. It is estimated that the symptoms affect 4 to 25% of fathers in the first two months of functioning in a new role. However, the pattern of depression in fathers is different from that of mothers – the axial symptoms of depression may be less visible, while men appear hostility or alcohol abuse. Etiological factors are little known. Among those that increase the risk of man's mood disorders after childbirth, the most common are maternal postpartum depression and the occurrence of other perinatal mental disorders, as well as socioeconomic risk factors (poverty, job loss).

The negative consequences of untreated postpartum depression in fathers affect both themselves and the family. Numerous longitudinal studies confirm that the symptoms of paternal depression, similarly as maternal depression, promote the occurrence of mental disorders and socio-emotional difficulties in children and adolescents.

Thus, it seems important to increase public awareness of paternal depressive mood disorders associated with the birth of a child, in particular among specialists involved in medical care for a man and family in the perinatal period. Prevention and early detection of

depression symptoms helps to provide appropriate pharmacological and psychological help, which can reduce or eliminate the negative effects of the disease.

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METABOLIC SYNDROME AND BENIGN PROSTATIC HYPERPLASIA

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Benign prostatic hyperplasia (BPH) is a cluster of abnormalities, which include benign prostatic obstruction (BPO), benign prostatic enlargement (BPE), bladder dysfunction (BD), and lower urinary tract symptoms (LUTS). Histologically, it is manifested by the proliferation of epithelial and prostate stromal cells. Clinically, BPH can lead to the narrowing of the urinary tract, and consequently to *bladder outlet obstruction* (BOO). As the world population is aging, the incidence of BPH and LUTS is rapidly increasing. Histopathological changes in this gland may affect as many as half of all men over 50 years of age, and this percentage increases by approximately 10% after each subsequent decade of life. Until now, pathophysiology of the BPH development has not yet been fully elucidated (*De Nunzio et al.*: Eur Urol. 2011, 60, 106–117; Chughtai et al.: Nat Rev Dis Primers. 2016, 2, 16031).

There are many risk factors for BPH: nonmodifiable (age, genetic determinants, race) and modifiable (sex hormones, hypertension, cardiovascular disease, obesity, diabetes, diet, bad eating habits, physical activity, inflammation) (Egan: Urol Clin North Am. 2016, 43, 289–297). The latter open up new possibilities of treatment and prevention. Risk factors for BPH also include metabolic syndrome (MetS), defined as coexistence of metabolic risk factors. Numerous studies indicate that many modifiable age-related metabolic disorders (MetS, obesity, dyslipidemia, diabetes) play an important role in the development and progression of LUTS and BPH. MetS and related changes in the levels of steroid sex hormones, as well as mild chronic inflammation contribute to the development of BPH (Vignozzi et al.: Nat Rev Urol. 2016, 13, 108–119; Ngai et al.: Asian J Urol. 2017, 4, 164–173).

Our results demonstrated that the majority of the BPH patients after transurethral resection of the prostate (TURP) had MetS. Moreover, in these cases, age, the levels of high density lipoprotein (HDL) cholesterol, insulin, sex hormone binding globulin (SHBG), as well as the levels of hormones: *luteinizing hormone* (LH), *dehydroepiandrosterone sulfate* (DHEA-S), and estradiol were significantly related to BPH. The patients with diagnosed

BPH had considerably higher levels of DHEA-S and lower levels of SHBG than their healthy counterparts. Lower levels of SHBG were also observed in the patients with BPH and concomitant MetS compared to the patients with BPH but without MetS (Grzesiak et al.: Clin Interv Aging. 2018, 13, 1375–1382; Grzesiak et al.: Int J Environ Res Public Health. 2019, 16, E1006).

The awareness of the relationship between MetS and the progression of BPH creates the possibility of proper treatment. What is more, the management of modifiable risk factors for MetS can delay or even prevent MetS complications, such as LUTS and BPH.

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IMPORTANCE OF DEHYDROEPIANDROSTERONE SULFATE ASSESSMENT IN MALES

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Dehydroepiandrosterone sulfate (DHEAS) is a sulfated form of dehydroepiandrosterone. Studies of large number of males with DHEAS pathology are infrequent. To perform an investigation of significance of DHEAS assessment in males of different ages.

Analysis of 3533 patients' (3013 females and 520 males) DHEAS assessment list was done. DHEAS was assessed 1.6–13.5 times more frequently in women than in men. A peak of DHEAS for women was around 25 years. In males, referrals for DHEAS were uniform during decades, excepting extremes of age (0–9 and 75+). DHEAS levels in 0–24 year-old females were higher than in males. After 40 years, DHEAS was statistically significantly higher in men than in women. Analysis of 491 case records showed low DHEAS in boys, aged 0–9 years and in men, aged 65–84. High DHEAS was detected as a peak at around 30 years, but never after 55 years. In patients with low DHEAS prevailed congenital adrenal hyperplasia – 31.3%, adrenal tumors – 29.8% and adrenal insufficiency – 19.3%. High DHEAS prevailed in patients with arterial hypertension – 26.4% and overweight/obesity/hypothalamic dysfunction – 18.8%. Seventy one woman and 117 men had adrenal tumors. Higher frequency of adrenal tumors was observed in women around their 30-ties. A peak of adrenal tumors frequency in men was around their 70-ties. We analyzed list of 3700 consecutive abdominal only and complex abdominal, chest and pelvic computer tomographies for the age and gender. A peak performance of computer tomographies in men and women coincided was between 65 and 74 years. This study permits to determine, what DHEAS pathology may be detected in males of different ages.

Marek Mędras

ANDROGENIC-ANABOLIC DOPING AS A SOCIAL AND MEDICAL PROBLEM

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The author presents problems arising from the abuse of androgenic-anabolic substances, in particular medical effects of this phenomenon. Particular attention is paid to changes in the hypothalamus-pituitary-gonadal system and the possibilities of therapeutic treatment in this area.

Andrzej Milewicz

OBESITY AND INFERTILE COUPLE – A ROLE OF INSULIN RESISTANCE

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Although both in obese women and men, disturbances of hypothalamus function, gonads or adipokines secretion are observed, these abnormalities are most common in insulin resistance cases. This impairment of tissue sensitivity to insulin is observed only in metabolic or abdominal obesity found in normal body mass patients. Insulin resistance is the key to the whole complex of hormonal or fertility disturbances in women with diagnosed polycystic ovaries. Insulin resistance coexisting with obesity is the reason for early miscarriages and small efficacy of reproduction supportive techniques. In extreme cases, bariatric procedures resulted in the increase of pregnancy numbers in obese women. In the case of male abdominal obesity, ejaculation volume was diminished and semen quality was restricted. Also, obesity has a negative impact on sex in both males and females. Metformin is a drug of choice in the case of insulin resistance treatment. It influences positively hormonal and metabolic disturbances as well as miscarriages in females and it also increases testosterone level and semen quality in males.

Jerzy Niedzielski

ADOLESCENT VARICOCELE – A CURRENT CLINICAL PROBLEM

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Varicocele are defined as abnormal widening of the veins of the pampiniforme plexus due to venous reflux. They occur in 14–20% of adolescents over 10 years of age and with a similar frequency in adulthood. They appear

mainly on the left side (78–93% of cases). The mechanism of formation of varicocele is not fully understood. The following factors are taken into account: accelerated body growth and increased blood flow through the testes during puberty, genetic factors, anatomical conditions (left side). Varicose veins can induce apoptotic pathways as a result of heat stress, lack of androgens and accumulation of toxic substances. Histopathological picture abnormalities, similar to those of infertile men, are found in 66% of teenagers with varicocele. In 70% of patients with grade II and III varicocele, a loss of left testicular volume was observed that resolved after adolescent varicocelectomy (76.4%). Approximately 20% of teenagers with varicocele have fertility problems and the adverse effect of varicocele increases with time. Improvement of sperm parameters was demonstrated after varicocelectomy in adolescents. Varicocele are usually asymptomatic, rarely cause pain, and are noticed accidentally by the patient or pediatrician during a routine visit. Scrotal ultrasound (Doppler-CW) allows to assess the size of both testicles, loss of testicular volume, the width of the pampiniforme plexus vessels (> 2mm) and the flow velocity of the reflux wave. Supranormal FSH (follicle-stimulating hormone) and LH (luteinizing hormone) responses to the LH-RH (luteinizing hormone - releasing hormone) stimulation test indicate testicular damage in a teenager with varicocele. There is no evidence that varicocelectomy in adolescents will provide a better andrological result than surgery performed later. Recommended indications for varicocelectomy in children and adolescents are: varicocele associated with the small testis, other testicular diseases affecting fertility, bilateral varicocele, pathological quality of sperm (in older adolescents), symptomatic varicocele. Surgical intervention involves ligation or occlusion of internal spermatic veins at different levels.

In conclusion, there is moderate evidence on the benefits of varicocele treatment in children and adolescents in terms of testicular volume and sperm parameters. Current evidence does not indicate superiority of any of the surgical / interventional techniques in terms of treatment success. Lymphatic sparing surgery significantly reduces the risk of hydrocele formation. Long-term treatment outcomes, including paternity and fertility, remain unknown.

Michał Radwan

METHODS FOR SELECTING SPERMS FOR IVF PROCEDURES

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The sperm's reproductive potential is due to many complex mechanisms. Various factors can have a negative impact on sperm's biochemical parameters, genetics and morphology. Currently, the standard semen analysis

according to the recommendations of the World Health Organization (WHO) is the analysis that best allows to assess a man's fertility. Over 25 years ago, intracytoplasmic sperm injection (ICSI) was introduced into daily practice. This fact was a real breakthrough in the treatment of male factor infertility. To date, several million children have been born in the world thanks to this method.

Unfortunately, despite the high effectiveness of this method, there are specific clinical situations in which the selection of a sperm with the Hofman's contrast microscope may not provide optimal treatment effectiveness. This is due to the fact that standard visualization of the sperm does not allow to fully assess the factors affecting fertilization and embryo development. Depending on the situation of each couple, the embryologist should consider additional methods for ICSI sperm selection. However, caution should be exercised because some sperm selection methods have not yet been proven effective. Their safety for the health of born children has not been clearly demonstrated either.

Ewa Rajpert-De Meyts

PATHOGENESIS OF TESTICULAR GERM CELL CANCER – LATEST NEWS

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Recent years have seen a great progress in the basic research and clinical management of testicular germ cell tumours (TGCT). The latest WHO classification (2016) recognized the origin and biological features of TGCT, which are now divided into two main groups: 1) TGCT derived from *germ cell neoplasia in situ*, GCNIS: seminoma and non-seminoma, which are by far most common, and 2) TGCT not related to GCNIS; including childhood germ cell tumours and spermatocytic tumour of older men. The incidence of testicular cancer has continued to increase, with spikes in Southern and Eastern Europe, and among American Hispanics, while in Northern Europe (incl. Denmark) the rates have slowed down (Gurney et al.: Eur Urol 2019 – in press). These changing trends are consistent with a strong influence of environment or lifestyle, but causal factors remain unknown. The environmental influence is modulated by genetic background, and Caucasian populations are at greatest risk. TGCT is a polygenic disease, with a striking paucity of oncogenic driver mutations, except rare mutations in *KIT* and *KRAS* (Litchfield et al.: Eur Urol. 2018, 73, 828–831), but with numerous significant susceptibility loci, mainly linked to sex differentiation and gonadal development, but also centrosome cycle and telomerase function, e.g. *KITLG*, *SPRY4*, *BAK1*, *DMRT1*, *TERT*, *GATA4*, *AMHR2* (Wang et al.: Nat Genet. 2017, 49, 1141–1147;

Pyle et al.: Abstract ACCR 2019; manuscript in preparation). The biological significance of these variants and the importance of possibly affected pathways is currently under investigation in independent validation studies, in human tissues, incl. ex vivo fetal testis cultures and in cell lines (Jørgensen et al.: Cell Reports. 2018, 25, 1924–1937; Das et al.: Andrology 2019, 4, 527–536).

Special biological features of TGCT, especially a high expression of embryonic pluripotency factors and more recently discovered specific micro-RNAs (miR-371a-3p), which can be detected in plasma/serum, can aid in diagnosis and monitoring of TGCT (Dieckmann et al.: J Clin Oncol. 2019, 37, 1412–1423). New miRNA-based tests are now very close to implementation in the clinics. Andrologists play an important role in the diagnosis and management of patients with TGCT, because of the association of this cancer with testicular dysgenesis and decreased fertility, as well as with post-treatment late effects, including hypogonadism.

Iwona Rotter

MALE FACE OF BEHAVIORAL ADDICTIONS

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Behavioral addiction is an addiction to impulses, such as gambling, the Internet, work, sex, shopping, a mobile phone or exercise. This addiction is associated with a strong need to repeat given activities, difficulties in controlling their performance, persistent repetition despite harmful consequences, putting these behaviors above other activities and the occurrence of a set of unpleasant symptoms (irritability, anger, aggression, etc.) when trying to stop or reduce these behaviors. The development of behavioral addictions is conditioned by psychological and environmental factors that overlap the biological background, including genetic predisposition. Considering the biological aspect, the reward system with its main neurotransmitter dopamine plays a key role in the formation of behavioral addictions. In the DSM V classification (The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association – Revision V) the term “addiction” has been replaced by the term “disorder” (Rowicka: Uzależnienia behawioralne. 2015, 6).

A Public Opinion Research Center (CBOS) report from 2015 indicates that the criteria for addiction to gambling were met by 5.3% of Poles over 15 years of age with a double of men (CEBOS Announcement, Warsaw, 2015). Internet addiction is much less common, but also in this case men prevail. A similar situation applies to cybersex addiction. In the case of shopaholism, female sex dominates, although in recent years an increase in the incidence of this problem has been observed in young men.

Men who meet the criteria of behavioral addictions are more likely to present aggressive behavior. In the etiopathogenesis of behavioral addiction and aggression, the role of monoamine oxidase A gene (MAOA) mutation is raised. This gene is located on the X chromosome. Lack of MAOA activity results in anti-social behavior and acts of violence.

Ireneusz Salata

EAA CLINICAL PRACTICE GUIDELINES – GYNecomastia EVALUATION AND MANAGEMENT

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Gynecomastia (GM) is a benign proliferation of the glandular tissue of the breast in men. Depending on the age and criteria used for the definition, the frequency of gynecomastia is 32–65%. GM of infancy and puberty are benign conditions resolving spontaneously in the majority of cases. In adult men GM is more prevalent among the elderly and proper investigation may reveal an underlying pathology in 45–50% of cases.

Based on a review of the articles in English, the European Academy of Andrology (EAA) expert group has developed guidelines for the assessment and management of gynecomastia in everyday clinical practice. Objective of the study was to provide clinical practice guidelines for the evaluation and management of GM. Evidence-based recommendations were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. Results was formulated in five statements and fifteen clinical recommendations.

The purpose of GM assessment should be the detection of: a) underlying pathological conditions, b) reversible causes (administration/abuse of aggravating substances), c) the discrimination from other breast lumps, particularly breast cancer. Assessment should comprise a thorough medical history and physical examination of the breast and genitalia (including testicular ultrasound). In the laboratory investigations we should determine the concentration of: testosterone, estradiol, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), prolactin, human chorionic gonadotropin (hCG), α -fetoprotein (AFP), liver and renal function tests. Breast imaging may be used whenever the clinical examination is equivocal. In suspicious lesions, core needle biopsy should be done. Watchful waiting is recommended after treatment of underlying pathology or discontinuation of substances associated with GM.

Testosterone treatment should be offered to men with proven testosterone deficiency. The use of selective

estrogen receptor modulators (SERMs), aromatase inhibitors and non-aromatizable androgens is not justified in general. Surgical treatment is the therapy of choice for patients with long-lasting GM.

Marta Skrodzka

IMPLANTATION OF PENILE PROSTHESIS – WHAT TO DO BEFORE IT TO OBTAIN SUCCESS?

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Penile prosthesis insertion is a last resort treatment in patients with end stage erectile dysfunction. Satisfaction rate is highest among all available treatment modalities. This however requires multistage preparations: appropriate patients' selection, partner involvement, detailed discussion regarding aims of the surgery and possible complications, choice of implant, technical pre-operative preparation and post-operative regimen. In view of 'irreversibility' of this technique all the conservative options should be exhausted, patient's expectations clarified and all the doubts addressed. In selected cases psychosexual counselling and non-standard preparation may be necessary. The lecture presents all these issues and discusses difficult cases.

Sławomir Sobkiewicz

A PLATFORM FOR COOPERATION BETWEEN ANDROLOGIST AND GYNECOLOGIST IN THE TREATMENT OF INFERTILE COUPLES

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Types of cooperation between gynecologist and andrologist are individual treatment for men and separately for women – doctors do not know about themselves and do not cooperate or cooperate with each other, sometimes as part of an infertility treatment clinic. The aim of the andrologist's diagnosis and treatment is to assess sperm parameters, assess the causes of sperm deficiency, and obtain sperm or improve sperm results. The aim of diagnostics and treatment by a gynecologist: determining the hormonal parameters of a woman, determining the patency of the fallopian tubes, endometrial assessment and assessment of the structure of the uterus and the occurrence of focal changes in the uterus. The most important goal of both doctors should be: getting pregnant and getting a child by a couple. That is why the cooperation of both specialties is so important – especially if it takes place outside the infertility treatment clinic.

Despite the development of modern means of communication, there is no permanent information exchange platform between andrologists and gynecologists and a platform for continuous education for gynecologists, urologists, endocrinologists, immunologists and other specialties dealing with infertility treatment.

Marta Sochaj

THE IMPACT OF HEALTH STATUS ON ERECTILE DYSFUNCTION IN MEN 40–80 YEARS OF AGE – THE RESULTS OF EUROPEAN MALE AGING STUDY

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The European Male Aging Study (EMAS), was a cross-sectional multicenter study, run in eight European countries, on a sample of 3369 randomly selected men, aged 40–79, conducted between 2002 and 2008 (Corona et al.: The J Sex Med. 2010, 7, 1362–1380). Blood samples were obtained together with anthropometric measurements and different surveys were evaluated, among others those concerning quality of life, lower urinary tract symptoms and sexual functions - a dedicated questionnaire was used (O'Connor et al.: J Sex Med. 2008, 5, 1374–1385). Around 30% of men reported erectile dysfunction and that was closely associated with age and concomitant comorbidities. More than 50% of all subjects reported one or more chronic comorbidities. Overall, hypertension (29%), obesity (24%) and heart disease (16%) were the most prevalent conditions. Most complaints about erectile dysfunction was reported in the 50–59 years age band. Men in transitional countries had a higher prevalence of morbidities and impairment of sexual function as well as lower quality of life. The presentation summarizes actual risk factors for erectile dysfunction in the European population, including a sexual function questionnaire EMAS – SFQ. It is a survey looking at multiple sexual dysfunction in opposition to a short but popular questionnaire of erectile dysfunction (IIEF-5, international index of erectile function).

Piotr Paweł Świniarski

IMPLANTATION OF PENILE PROSTHESIS – WHAT TO DO AFTER IT TO OBTAIN SUCCESS?

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The final success of the implantation of penile prosthesis (IPP) depends on many factors: pre-op patient

preparation, correct and uncomplicated implantation and proper follow-up. Post-op time shortly after surgery requires antibiotics prophylaxis, catheterization and drainage, compressing dressing on penile and scrotal area, appropriate inflation and afterwards deflation of cylinders and implant position control. During first few weeks and months after surgery next few things are crucial: control of wound healing, post-op pain and physiological micturition recovery. After complete wound closure (6 weeks) is time for couple education how to inflate and deflate penile prosthesis and to make their sexual expectations more realistic and first experience with IPP positive. During follow-up period it is important to be sensitive for the „red alert” which require revision, removal or exchange of penile prosthesis. It is important to underline not only the surgeon, but the role of GP (general practitioner) or the urologist who sent patient in the process of follow-up.

Sylwia Szpak-Ulczo

EXCESS OF ANDROGENS IN MEN

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Endogenous excess of androgens in men is a relatively rare phenomenon. It can originate from adrenal tumors, both benign and malignant. Adrenal adenomas, secreting only androgens are rare. More often it is mixed secretion with glucocorticosteroids. Similarly, adrenocortical carcinomas secreting only androgens are rare, while the mixed nature of hormonal activity (androgens + glucocorticosteroids) is more common. Elevated androgen concentrations also occur in some adrenal steroid blocks, for example congenital adrenal hyperplasia from 21-hydroxylase or 11- β -hydroxylase deficiency. Some of them are detected immediately after birth, because they manifest as life threatening electrolyte disturbances. Other cases are recognize when fertility problems are diagnosed. Excess of androgens can also come from hormone-secreting testicular tumor. Tumor from Leydig cells can secrete testosterone and androstenedione. LH-secreting tumors of pituitary gland, which lead to elevated testosterone level, are extremely rare causes of androgen excess.

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WHAT IS IN A SPERM FLAGELLAR BEAT?

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Computer Aided Sperm Analysis (CASA) introduced new and objective methodologies to analyse sperm motility among others, and provide an array of new parameters and sperm functional tests such as sperm mucous penetration and hyperactivation. In this investigation the focus is on new approaches in sperm motility analysis of diverse mammalian species

Despite the great advances made in the broad field of CASA, we need to assess what has been measured. Firstly, the X and Y coordinates of head centroid movement are tracked to calculate sperm tracks and associated kinematics. This analysis ignores two important aspects, namely, that sperm does not swim two dimensionally and essentially ignores the Z axis (3D) and that the head determines the trajectory instead of the flagellum which actually “pushes the head”. Van der Horst and Sanchez (2016) partly solved the problem of 3D movement by using a simple mathematical model of X and Y coordinates and then extra-polated the Z coordinate by assuming the sperm moves in spherical helix. This approach is useful to visualize the 3D pattern of movement but is still based on head centroid movement. The Birmingham Group (above) developed a unique software programme called FAST (Flagellar and Sperm Tracking) that allows detailed flagellar analysis at high frame rates. In this study we tested the applicability of FAST and its relationship to traditional CASA of Tankwa goats, Swakara rams, laboratory mice, vervet monkeys and humans.

Sperm motility was captured using negative phase at 169 fps in 10 μ m deep Leja slides in different media using the SCA 6.4 CASA system. Several fields were captured and exported as avi files and then analysed in FAST for flagellar analysis.

We found that while traditional SCA CASA and FAST may be complimentary, flagellar analysis opens a new window to describe new parameters of sperm flagellar movement using pure applied mathematics and physics principles such as the energy output in watts per sperm and this together with other sperm functional tests provide new insights and potentially new applications in fertility assessment.

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THE ROLE OF AROMATASE AND ESTROGEN RECEPTORS IN PHYSIOLOGICAL AND DISTURBED SPERMATOGENESIS

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It has been known that male gonads are both a source of estrogen production and a target organ of their action. At the nuclear level they exert their activity through two classic nuclear receptors ESR1 (estrogen receptor 1) and ESR2 (estrogen receptor 2) and a membrane G protein-coupled estrogen receptor 1 (GPER). Estrogen receptors and the aromatase enzyme are present in both seminiferous tubules and intertubular spaces, indicating the direct regulatory role of estrogens in both steroidogenesis and spermatogenesis (Dostalova et al.: Int J Mol Sci. 2017, 18 (5), E904).

There are a number of studies analyzing the immunohistochemical localization and mRNA expression for ESR1 and ESR2 as well as aromatase in the testes of men with normal and impaired spermatogenesis. Some of them indicated that in testicular biopsies presenting a given type of damage there are differences in the expression of aromatase and/or ESR1 and ESR2 genes. Unfortunately, no data are available for GPER expression in human testicular tissue with impaired spermatogenesis. The single studies for GPR30 were conducted in gonads with normal spermatogenesis, with testicular tumors, or in patients with Klinefelter syndrome.

In our study, we evaluated the expression of aromatase and estrogen receptors genes in seminiferous tubules obtained after laser microdissection from testicular biopsy with normal and impaired spermatogenesis. The obtained results were the analyzed in relation to subjects' hormonal status and Sertoli cell function/maturation. We have shown an increase in GPER receptor gene expression in seminiferous tubules with impaired spermatogenesis. In addition, analysis of correlations revealed the existence of a positive relationship between the increase in GPER gene expression and the expression of Sertoli cell maturity markers and serum FSH concentration, which may suggest the involvement of GPER in regulation of Sertoli cells' function and maturation.

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Jan K. Wolski

MALE OXIDATIVE STRESS INFERTILITY (MOSI) – A NEW LOOK AT THE KNOWN PROBLEM

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During the first year of regular intercourses without any contraceptive, 76–85% of couples get spontaneously pregnant. Infertility is defined by the World

Health Organization as an inability to have this biological standard. WHO reports shows that more than 190 million people struggle with the problem of infertility, which is a significant social problem. The analysis of the causes of male infertility indicates that despite significant advances in knowledge of reproduction, among 50% of men are not found to cause a decline in fertility – described as idiopathic infertility. A multi-center study conducted under the direction of Ashok Agarwal has shown that oxidative stress (OS) plays an independent role in male infertility etiopathogenesis. It is estimated that 30–80% of infertile males are found to have elevated concentrations of reactive oxygen species in semen. This significantly reduces the potential for fertility through negative impacts on metabolic pathways, including interference with capacitation and possible damage to sperm membrane and DNA, which may impair the sperm's potential to fertilize an egg and develop into a healthy embryo. Proper diagnosis of male reproductive potential should therefore include an assessment of sperm oxidative stress. The researchers propose the term of these disorders - MOSI (male oxidative stress infertility), as a new descriptor for the diagnosis of infertile males with abnormal semen and OS properties, including many patients who were previously classified as idiopathic infertility. The oxidation reduction potential of ORP (oxidation-reduction potential) can be a useful clinical biomarker for the classification of MOSI, because it takes into account the levels of both oxidants and reductants (antioxidants). Current treatment protocols for OS, including the use of antioxidants, are not evidence-based and have potential complications, associated with increased health-related expenditure. The EBT (evidence-based treatment) principle uses easy, repeatable and cost-effective tests to measure ORP, which can provide a more targeted, reliable approach to the use of antioxidants, while minimizing risk overdose.

Wojciech Zgliczyński

PITUITARY TUMOR AS A CAUSE OF HYPOGONADISM

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Nowadays, frequency of detected findings inside *sella turcica* increases, due to development of endocrine and neuroradiological diagnostic procedures. Estimated frequency of these findings in autopsy tests in unselected material reaches 24%. Within *sella turcica* can be found: tumours (mostly adenomas), cysts, infiltrative and inflammatory lesions. These findings are often accidentally revealed (*incidentaloma*), without any clinical manifestation. It has been assumed, that the most common symptom of a pituitary tumour in adults is secondary

hypogonadism, caused by low secretion of gonadotropins, due to impaired secretion of the hypothalamus gonadotropin-releasing hormone (GnRH) with increased prolactin (PRL) or adrenocorticotropic hormone (ACTH) levels, and as a result cortisol. Disabled pituitary gonadotropic cells also occur as a result of tumour compression or anterior pituitary gland cells growth, haemorrhage, or inflammatory infiltration. Diagnostics of the hypogonadism pathomechanism in the *sella turcica* tumours is based on magnetic resonance imaging (MRI) and hormonal tests. Treatment in these cases involves pharmacological control of hyperprolactinemia or surgical tumour removal.

Birute Zilaitiene

**MANAGEMENT OF
OLIGO-ASTHENOTERATOZOOSPERMIA:
NEW EVIDENCES**

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Oligoasthenoteratozoospermia (OAT) is a frequently reported diagnosis in men from infertile couples and there are still a lot of controversies on the mechanisms of this spermatogenesis impairment and management possibilities. OAT is diagnosed when total number of spermatozoa in the ejaculate, percentage of progressive motility and normal morphology spermatozoa are below the lower reference range (but spermatozoa are present in the ejaculate).

For physical examination signs of hypogonadism and scrotal investigation to assess testicular and epididymis consistence, volume, presence of varicocele, deferential ducts should be performed. It is recommended to perform scrotal ultrasound (US) as part of routine investigation of men with OAT (Colpi et al.: *Andrology*. 2018, 6 (4), 513–524). In the case of OAT risk for testicular cancer is 11.9 times higher if compare to normozoospermia

(Hanson et al.: *Fertil Steril*. 2016, 105 (2), 322–328). The highest value of scrotal US: to exclude a testicular cancer or testicular microlithiasis when a physical examination did not show any abnormality, to confirm a varicocele suspected at physical evaluation and when a genital tract obstruction is suspected.

Hormonal status should be evaluated in all men with OAT, including serum testosterone, LH, FSH. FSH > 10 IU/L has a predictive power of 85.7% to detect a sperm count < 20×10^6 /mL (Jensen et al.: 1997). Serum sex hormone-binding globulin and prolactin is added if hypogonadism is suspected, TSH – if there are signs of thyroid pathology.

For the treatment of OAT FSH can be suggested with low evidence in men with idiopathic oligozoospermia or OAT to improve quantitative and qualitative sperm parameters and pregnancy rate. There is not enough evidence to suggest treatment of OAT with antioxidants and antiestrogens or aromatase inhibitors (Colpi et al.: *Andrology*. 2018, 6 (4), 513–524). Hypoandrogenism treatment with androgens is recommended only when infertility treatment is completed due to negative effect of exogenous androgens on endogenous testosterone production and spermatogenesis.

Therefore, the authors suggested the use of clomiphene 50 mg or tamoxifen 20–30 mg daily for 3–6 months and to proceed with assisted reproduction techniques (ART), if no pregnancy has been achieved (Chua et al.: *Andrology*. 2013, 1 (5), 749–757). Genetic tests include karyotype analysis and microdeletions in the long arm of chromosome Y (Yq) – AZF deletions. Karyotype analysis is recommended for infertile men with a sperm concentration $\leq 5 \times 10^6$ /mL. Cystic fibrosis transmembrane conductance regulator (CFTR) gene evaluation is recommended in case of suspicion for incomplete congenital obstruction of the genital tract.

Surgical methods may help to remove a cause of spermatogenic impairment – varicocele, intraprostatic cyst, ejaculatory duct stenosis correction. Assisted reproduction techniques are used in the case other options are not available or not effective.