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SYMPOSIUM OF SCIENTIFIC TRANINING OF THE POLISH SOCIETY OF ANDROLOGY – 19th DAY OF ANDROLOGY

Cracow 17–18.11.2017 www.pta2017.pl

Report

The Conference of the Polish Society of Andrology – 19th Day of Andrology took place on November 17–18, 2017 in the Qubus Hotel in Cracow. The Conference was organized by the Foundation for the Medical University of Lodz (FUMED) with the Organizing Committee led by prof. Barbara Bilinska and the Scientific Committee chaired by prof. Jolanta Slowikowska-Hilczer.

The meeting was preceded by an exam of clinical andrology. It was organized for the first time by the Polish Society of Andrology. All 24 attending physicians passed the exam and received a PTA Certificate in clinical andrology.

The scientific part of the Conference was started by the President of the Polish Society of Andrology and the Chairman of the Scientific Committee, prof. Jolanta Slowikowska-Hilczer and the Chairperson of the Organizing Committee prof. Barbara Bilinska from the Department of Endocrinology, Institute of Zoology, Jagiellonian University in Cracow. Short speeches were given by prof. Wojciech Nowak, Rector of the Jagiellonian University, and dr. Dariusz Koscielniak, representative of the Medical Chamber in Cracow, who honored the Conference with their presence. Award named by prof. Michal Bokiniec for the Young Polish Scientist in andrology for 2016 received dr. Katarzyna Chojnacka from the Jagiellonian University in Cracow. The winner presented the awarded work in the short presentation.

The first lecture was given by prof. Rafal Kubiak from the Department of Medical Law of the Medical University of Lodz on the rights of patients to intimacy and respect for human dignity. In the academic sessions lectures were delivered by prof. Ewa Rajpert-De Meyts from Denmark, prof. Aleksander Giwercman and prof. Yvonne Lundberg-Giwercman from Sweden, prof. Gerhard van der Horst from South Africa, prof. Birute Zilajtiene from Lithuania and dr. George Kanakis from Greece, a delegate from the Greek Society of Andrology. In addition, lectures were delivered by many excellent lecturers from Poland. Issues related to male fertility, male genital infections, the influence of environmental factors on the male genitals function were covered. Diagnostic methods and therapeutic options in infertility have also been discussed, as well as sexual abnormalities in men, prostate diseases, testicular neoplasms and penile disorders. Representatives of basic sciences presented the results of their latest research related to the physiology and pathology of the male genitals. The session of short scientific presentations was also very popular.

The meeting ended with the invitation of the President of the Polish Society of Andrology to the next Conference of the Polish Andrological Society in 2018 in Lublin.

Abstracts of lectures

Piotr Chłosta

PROSTATECTOMY AND ITS COMPLICATIONS

Chair and Department of Urology, Jagiellonian University Medical College, Cracow, Poland; e-mail: piotr.chlosta@uj.edu.pl

Radical retropubic prostatectomy is a surgical procedure in which the prostate gland is removed through an incision in the abdomen. It is most often used to treat individuals who have early prostate cancer. Radical retropubic prostatectomy can be performed under general, spinal, or epidural anesthesia and requires blood transfusion less than one-fifth of the time. Radical retropubic prostatectomy is associated with complications such as urinary incontinence and impotence, but these outcomes are related to a combination of individual patient anatomy, surgical technique, and the centre experience and surgical skills of urologist.

The most common serious complications of radical retropubic prostatectomy are loss of urinary control, erectile dysfunction, urethral strictures and lymphocele. As many as forty percent of men undergoing prostatectomy may be left with some degree of urinary incontinence, usually in the form of leakage with sneezing, etc. (stress incontinence) but this is highly surgeon-dependent. Impotence is common when nerve-sparing techniques are not used. Although erection and ejaculation are affected, penile sensation and the ability to achieve orgasm remain intact. Therefore, use of medications such as sildenafil, vardenafil or tadalafil may restore some degree of potency when the cavernous nerves remain functioning.

Continence and potency may improve depending on the amount of trauma and the patient's age at the time of the procedure, but progress is frequently slow. Potency is greatly affected by the psychological attitude of the patient. Erectile dysfunction outcomes can be predicted by intraoperative cavernous nerve electrical stimulation with a penile plethysmograph.

Przemysław Dudek

PROSTATITIS

Department of Urology and Urologic Oncology, University Hospital in Cracow, Poland; e-mail: przemekdudek@o2.pl

Prostate inflammation is caused by a bacterial infection. It is also necessary to remember about other types of inflammation and pelvic pain syndrome, which should be distinguished from acute and chronic bacterial infections. Pathogens are routinely detected only in 5–10% of cases, which is the basis of rational therapy. The remaining patients are treated empirically. *Escherichia coli* is a predominant microorganism responsible for acute inflammation, but the spectrum of pathogens is much broader in chronic inflammation. The main symptoms are pain and discomfort of the lower urinary tract. In palpation the prostate is tender and swollen, but may also be unchanged in chronic inflammation. In order to plan treatment (especially targeted), medium urine cultures (acute inflammation) and the Meares-Stamey's test should be performed in the case of chronic inflammation. Transrectal ultrasonography is reserved only in cases with suspicion of prostate abscess. Acute bacterial prostatitis is a serious disease manifesting in high fever, often with chills and severe pain. Antibiotics are administered parenterally. Therapy is maintained for 2–4 weeks in acute inflammation and 4-6 weeks in chronic inflammation. About 10% of men with acute prostatitis report urine retention. In such cases, suprapubic cystostomy, catheterization or intermittent catheterization should be proposed. However, other types of inflammation of the prostate – non-bacterial inflammation collected under the name chronic pelvic pain syndrome, which is divided into inflammatory, non-inflammatory and asymptomatic, should also be remembered. Useful during the differentiation of these states is the test of two glasses, sexual function questionnaires, evaluation of urethral flow, urinary retention after micturition and cytology. Treatment is multidirectional and depends on the dominant symptoms. Therapeutic uses include alpha-blockers, anti-inflammatory drugs, miorelaxants. It is recommended to change the lifestyle and give the psychological support. Treatment of prostate inflammation is still a challenge. In the US alone in 2000, diagnosis and treatment amounted to $ 84 million.

Emila Dziewirska[1], Renata Walczak-Jędrzejowska[2], Joanna Jurewicz[1], Katarzyna Marchlewska[2], Elżbieta Oszukowska[3], Jerzy Niedzielski[4], Wojciech Hanke[1], Paweł Kałużny[1], Jolanta Słowikowska-Hilczer[2]

EXPOSURE TO ENVIRONMETAL FACTORS – SEMEN PARAMETERS AND REPRODUCTIVE HORMONES LEVELS IN YOUNG POLISH MEN – PRELIMINARY RESULTS

[1]Department of Environmental Epidemiology, Nofer's Institute of Occupational Medicine, Lodz; [2]Department of Andrology and Reproductive Endocrinology, Medical University of Lodz; [3]II Clinic of Urology, Medical University of Lodz; [4]Department of Pediatric Surgery and Urology, Medical University of Lodz, Poland; e-mail: emila.dziewirska@imp.lodz.pl

The problem of the lack of offspring affects nearly every fifth couple at reproductive age in Europe. A male factor is exclusively responsible in about 20% of infertile couples and contributes in another 30–40% of couples. Many environmental factors and life style may affect male fertility. The aim of our study was to investigate the influence of different lifestyle and environmental factors on male reproductive health.

Participants were 209 young (19–30 y) men from general population. They completed detailed questionnaires on health quality and life style. Semen, urine and blood samples were collected. Basic semen parameters (concentration, total motility, sperm morphology) and the levels of reproductive hormones (testosterone, estradiol, FSH, LH, inhibin B, AMH, prolactin and SHBG) were obtained. In 150 urine samples the concentrations of triclosan, bisphenol A, oxybenzone and parabens were measured. The mean ±SD levels of these substances were: triclosan 3,98 ng ±112,18; bisphenol A 1,75 ±4,33; oxybenzone 7,33 ±58,34; methylparaben 13,27 ±81,33; ethylparaben 1,11 ±21,12; butylparaben 0,58 ±6,21.

The mean (±SD) age and BMI were 24,3 ±3,1 years and 23,75 ±1,2 kg/m^2, respectively.Most men had secondary education (51,8%) and were nonsmokers (78,1%). The mean (±SD) values for sperm concentration, motility and morphology were 43,3 mln/mL ±2,8, 54,3% ±1,5 and 3,9% ±1,8 respectively. The mean (±SD) levels of reproductive hormones were: FSH 2,1 ±1,9 mIU/mL, LH 3,2 ±1,6 mIU/mL, testosteron 16,1 ±1,5 nmol/L, estradiol 62,6 ±1,4 pmol/L, inhibina B 209,6 ±1,7 pg/mL, AMH 10,4 ±1,5 ng/mL, prolaktyna 10,5 ±1,6 ng/mL and SHBG 28,5 ±1,5 nmol/L. Preliminary regression model reveal that total sperm concentration was negatively associated with the level of FSH and estradiol (p = 0,021 and p = 0,012, respectively) which is consistent with previous studies conducted by other authors. Further analysis are necessary to clarify the association between environmental exposure and male reproductive health.

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Monika Frączek[1], Małgorzata Piasecka[2], Maciej Kurpisz[1]

PATHOGENETIC MECHANISMS OF BACTERIAL SEMEN INFECTIONS IN HUMAN. POTENTIAL INFLAMMATORY BIOMARKERS IN SEMEN

[1]Institute of Human Genetics in Poznan, Polish Academy of Sciences; [2]Department of Histology and Developmental Biology, Pomeranian Medical University in Szczecin, Poland;
e-mail: monika.fraczek@igcz.poznan.pl

Bacterial infections in the male urogenital tract are a growing problem of modern andrology. The prolonged infections that occur without any distinct clinical symptoms usually convert into a chronic subclinical process which is difficult to be identified in the current routine seminological diagnostics. In few previous experimental and clinical reports, the role of some pathogens in decreasing sperm fertilizing potential was highlighted. In these studies, apoptosis and oxidative stress were the most often suggested as potential mechanisms responsible for the male subfertility/infertility associated with local bacterial infections. Conducting comprehensive research using microscopic and molecular techniques in two independent research models, i.e. in different phases of semen bacterial infection *in situ* and in the own model of bacterial semen infection *in vitro*, resulted in a characteristic picture of subcellular changes in ejaculated human sperm. The data obtained indicated etosis connected with the elimination of male gametes by inflammatory cells as a new process that may also be involved in the mechanism of impairment of the structure and function of human spermatozoa in infectious environment.

The study for the first time has shown the destructive effect of coagulase-negative *Staphylococci* and anaerobic gram-negative rods on sperm cell membrane integrity as well as sperm mitochondrial energy metabolism with direct consequences for their fertilizing potential. In the light of the results obtained, the evaluation of membrane asymmetry as well as mitochondrial potential of germ cells may become a useful tool in the early diagnosis of asymptomatic bacterial semen infection, whereas the determination of lipid peroxidation level in semen can constitute a basis for the qualification of some patients for antioxidant supplementation, and may be a useful biomarker for monitoring the effectiveness of such therapy and restore the redox balance in semen.

On the one hand, the results obtained expanded our knowledge on the etiopathogenesis of semen bacterial infections. On the other hand, they may contribute to changes in the perception of asymptomatic bacteriospermia, especially caused by saprophytic strains, in clinical andrological practice.

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Kamil Gill[1], Aleksandra Rosiak[1,5], Joanna Jakubik[1], Michał Kupś[4,5], Łukasz Patorski[1,3], Rafał Kurzawa[2,5], Małgorzata Piasecka[1]

HUMAN SPERM CHROMATIN MATURITY AND ICSI OUTCOMES

[1]Department of Histology and Developmental Biology; [2]Department of Procreative Health, Pomeranian Medical University in Szczecin; [3]Department of Gynecology, Endocrinology and Gynecological Oncology, SPSK1, Pomeranian Medical University in Szczecin; [4]Department of Urology an Oncological Urology, Regional Specialist Hospital in Szczecin; [5]VitroLive Fertility Clinic in Szczecin, Poland;
e-mail: kamilgill@wp.pl.pl

Because sperm chromatin maturity may play a key role in reproductive success (*Bounartzi et al*.: Hum Fertil (Camb)., 2016, 19, 56-62), we verify the possible associations between sperm chromatin maturity, embryo development and the ability to achieve pregnancy. Evaluation of sperm

chromatin maturity using aniline blue (AB), toluidine blue (TB) and chromomycin A3 (CMA3) staining were carried out in a group of healthy volunteers with normozoospermia (n = 162) and males from infertile couples (n = 209) that underwent intracytoplasmic sperm injection (ICSI).

Low levels of sperm chromatin abnormalities (<16%) were found in most subjects (>50%). Statistically significant differences between men from infertile couples and healthy volunteers were noted only in the TB test (median: 12.00 vs. 10.00%). Moreover, a higher percentage of TB-positive sperm cells was discovered in the men from couples who achieved ≤50% fertilized oocytes compared to men who achieved >50% (median 18.00 vs. 12.00%). No significant differences were observed by the applied tests between the men from couples who achieved ≤50% and those who achieved >50% high-quality embryos on the 3rd or 5th day after fertilization, nor between the men from couples who achieved pregnancy and those who failed. The sperm chromatin maturity did not correlate with the ICSI results. However, the ROC (receiver operating curve) analysis revealed a significant predictive value of TB-positive spermatozoa only for fertilization (AUC = 0.705). Therefore, the TB assay can be considered as a useful test for the prediction of fertilization.

Our findings suggest that the level of sperm chromatin abnormalities of the examined men was not clinically significant. No found associations between sperm chromatin maturity and embryo development and the ability to achieve pregnancy. We could not exclude the effects of the repairing processes in the fertilized oocyte. The use of complementary tests that verify the status of the sperm chromatin seems justified.

The study was supported by Pomeranian Medical University in Szczecin (projekt nr WNoZ-322-04/S/2016, FSN-322-5/2016),

Aleksander Giwercman, Olof Ståhl, Patrik Romerius, Yahia Al-Jebari

HEALTH RISKS IN CHILDREN OF MEN TREATED FOR CANCER

Reproductive Medicine Centre and Molecular Reproductive Medicine Research Unit, Department of Translational Medicine, Lund University, Malmö, Sweden; e-mail: aleksander.giwercman@med.lu.se

Increasing proportion of men treated for cancer in childhood and young adulthood are cured for their malignancy. Thus, the issue of their reproductive function gains an increasing interest. In this context, one of the important aspects is the question of health of children fathered by men who have been treated for cancer.

Cancer therapies, as irradiation and cytotoxic drugs, are potentially mutagenic. An increased proportion of spermatozoa with chromosome aberrations was found in ejaculates of men treated, with chemotherapy for Hodgkin's lymphoma. We found increased proportion of sperms with DNA strand breaks in men who have been treated for testicular or childhood cancer, following irradiation but not chemotherapy (*Ståhl et al.*: Hum Reprod., 2006, 12, 3199–3205; *Romerius et al.*: Clin Cancer Res., 2010, 16, 15, 3843–3850). Although it has been reported that such DNA strand breaks hamper fertility *in vivo* as well as when standard *in vitro fertilization* is applied, this effect can be bypassed by use of *intracytoplasmic sperm injection* and the impact on the health of the offspring is unknown.

In a Danish-Swedish register study, including almost 2 million singletons, we found more than 15% increased relative risk of congenital malformations among children fathered by men who have been treated for cancer (*Ståhl et al.*: J Natl Cancer Inst., 2011, 103, 5, 398–406). One can ask whether this was due to the mutagenic effects of cancer treatment on sperm chromosomes or rather related to the cancer disease *per se?* Therefore, we looked at the risk of congenital malformations in newborns born before paternal cancer diagnosis (*Al-Jaberi et al.*: in manuscript). We found a statistically significant increase in the malformation rate of same magnitude as the one found in offspring conceived after the father was diagnosed with cancer. Our data indicate that children of men who have been diagnosed with malignancy have increased risk of congenital malformations but this increase, due its magnitude, is more of biological than clinical significance. Although the biological mechanism needs to be clarified, it seems that cancer in fathers and malformations in the offspring share etiological factors, genomic instability leading to both adverse conditions being one of candidates.

Yvonne Lundberg Giwercman

TESTOSTERONE AS RISK FACTOR FOR PROSTATE CANCER AND MORTALITY

Department of Translational Medicine, Lund University, Malmö, Sweden; e-mail: Yvonne.Giwercman@med.lu.se

Ever since 1941, when it was reported that testosterone drives growth of prostate cancer (PCa) (*Huggins* and *Hodges*: J Urol., 2002, 168, 1, 9–12), androgens have been considered as driving the disease and androgen ablation by chemical or surgical castration is therefore a cornerstone in the treatment of advanced PCa. However, population based studies have not shown any association with serum testosterone or its more potent metabolite 5α-dihydrotestosterone and PCa, and a meta-analysis of 18 prospective studies including almost 4000 men with incident PCa and more than 6000 control subjects found no evidence that high androgen concentrations were associated with excess PCa risk (*Endogenous et al.*: J Natl Cancer Inst., 2008, 100, 3, 170–183). Low serum testosterone has also in some studies been linked to all-cause mortality, whereas others reported no such association. Common to all these studies was that the

participants were older men and the follow up time was at most 10 years.

In order to evaluate the risk for PCa and mortality after a longer time period, we analysed all samples from men, 20–87 years of age, coming for baseline endogenous testosterone measurement during the period 1987–92 to the Department of Clinical Chemistry, Skane University Hospital, Malmö, Sweden and retrieved data concerning PCa diagnosis and cause of death by linking personal identification numbers with the Swedish Cancer Registry, the Swedish Cause of Death Registry, and the Population Registry as of December 2013.

After more than two-decades follow-up, we found no evidence that testosterone is a risk factor for PCa. On the contrary, those with highest serum concentrations seemed to have a lower risk, as had those with very low testosterone (*Bentmar Holgersson et al.*: Eur Urol, 2017, 71, 6, 992–994). However, being under the age of 50 years and having low testosterone, was linked to all-cause mortality (*Bentmar Holgersson et al.*: Eur Urol., 2017, 71, 6, 99–1992).

Katarzyna Gronostaj

TESTICULAR CANCER

Department of Urology and Urologic Oncology, University Hospital in Cracow, Poland; e-mail: katarzynagronostaj@gmail.com

Testicular cancer represents 1.6% of male neoplasms. It is the most common malignant disease among young adults. The predominant histopathology is germ cell tumor. This disease show excellent cure rate with average 5-year survival rate of 90%. The success of treatment is based on early diagnosis, careful staging, adequate treatment, multidisciplinary approach and strict follow up. Therapy is based on risk-adapted strategy. In non-advanced disease management aims at maintaining good results while reducing treatment-related toxicity. Treatment decisions are guided by the individual risk profile for tumor recurrence. More advanced stages require multidisciplinary treatment including radiotherapy, chemotherapy and surgery. The first line treatment depends on histopathology of primary tumor and the International Germ Cell Cancer Collaborative Group (IGCCCG) risk group. The review summarizes state of the art management of patients with testicular cancer.

Laura Grześkowiak

INFLUENCE OF CHRONIC COLITIS ON THE PROCESS OF SPERMATOGENESIS AND FERTILIZATION

Private Clinic Certus, Poznan, Poland; e-mail: laura.grzes@gmail.com

In about 40% of couples diagnosed with infertility, a significant decrease in fertility potential or infertility are on the male side. In numerous situations, azoospermia and oligozoospermia are connected with systematic diseases which occur on the basis of immunological disorders related to the alimentary tract. The main issue in a medical record is defecation disorders and changes in feces' character, whereas in mucosa tissue collected in proctoscopy or colonoscopy histopathological evaluation, chronic inflammation of various degree is found.

In a 6-month-long observation of men, during a nutritional and pharmacological treatment and modification of living conditions, the recovery of clinical symptoms and significant improvement of semen parameters were observed. As a result, 30% of couples got pregnant, despite remarkably impaired semen parameters in the initial evaluation.

Anna Hejmej[1], Ewelina Górowska-Wójtowicz[1], Alicja Kamińska[1], Laura Pardyak[1], Małgorzata Kotula-Balak[1], Joanna Dulińska-Litewka[2], Piotr Laidler[2], Barbara Bilińska[1]

NON-GENOMIC ACTION OF 2-HYDROXYFLUTAMIDE IN PROSTATE CANCER CELLS: AN IN VITRO APPROACH

[1]Department of Endocrinology, Institute of Zoology and Biomedical Research, Jagiellonian University, Kraków, Poland; [2]Chair of Medical Biochemistry, Jagiellonian University Medical College, Kraków, Poland; e-mail: anna.hejmej@uj.edu.pl

Cadherins and catenins are major contributors to cell-cell adhesion, playing crucial roles in maintaining integrity and homeostasis in adult prostate. Alterations in these proteins are involved in a number of important phenomena related to prostate cancer progression, including invasiveness of tumor cells and metastasis.

The present study aimed to investigate the effects of model anti-androgen 2-hydroxyflutamide (HF) on E-cadherin, N-cadherin and β-catenin phosphorylation in prostate cancer cell lines and to reveal signaling pathways that mediate these effects.

Androgen-sensitive human prostate cancer cell line (LNCaP) and androgen-independent prostate cancer cell line (PC3) were incubated with HF, testosterone, HF plus testosterone or HF plus inhibitors of two signaling pathways: mitogen-activated protein kinases/extracellular signal-regulated kinases 1/2 pathway (MAPK/ERK1/2) and phosphatidylinositol 3-kinase/Akt kinase pathway (PI3K/Akt). Expression, phosphorylation and localization of cell adhesion proteins and protein kinases were analyzed using western blot and immunocytochemistry, respectively.

We have demonstrated that in LNCaP cells HF induced rapid increase of E-cadherin phosphorylation at Ser 838/840 in MAPK/ERK1/2-dependent manner. In PC3 cells HF decreased Tyr 860 N-cadherin and Tyr 654 β-catenin phosphorylation and induced N-cadherin delocalization, acting via both MAPK/ERK1/2 and PI3K/

Akt pathways. It should be highlighted, that activation of MAPK/ERK1/2 and PI3K/Akt pathways, as well as the interaction between these pathways were differentially influenced by HF in LNCaP and PC3 cells.

Our findings expand the role of anti-androgen into non-genomic signaling, creating a link between anti-androgen action, activation of protein kinase pathways and phosphorylation of adherens junction proteins in prostate cancer cells.

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Gerhard van der Horst

DO ANIMAL SPERMATOLOGY MODELS HELP US TO UNDERSTAND HUMAN FERTILITY?

Department of Medical Bioscience, University of the Western Cape, Bellville, South Africa; e-mail: gvdhorst7@gmail.com

There are many approaches to try and establish the most suitable animal model(s) for human reproduction in general and sperm in particular. One generic approach is genomic; this refers to the overlap in DNA sequences among and within species. It is not surprising that sub-human primates share 95% to 98% of the human genome. However, it is surprising that cats share 90%, mouse 75% (but 90% of the mouse genome could be lined up with a region on the human genome) and even fruit flies sharing 47% of our genome. This makes the potential choice of animal sperm models even at the level of invertebrates quite large. A second approach involves for example searching for specific sperm functional tests that relate directly to fertility outcome such as hyperactivation and seems to occur in almost all animal species. A third approach is the aspect of monogamy and accordingly a lack of sperm competition. In this context it is assumed that humans have been shown to be monogamous during the last 25000 years. The main aim of this paper is to show which sperm models are applicable to human spermatology and potentially assist to understand human fertility better.

Sperm functionality particularly related to sperm hyperactivation in different species and animals where there is a lack of sperm competition are two approaches followed in this investigation. Hyperactivation in human, vervet monkey, bull, ram, goat, elephant, rhinoceros and some invertebrate species have been induced with caffeine, progesterone and procaine hydrochloride media and evaluated using Computer Aided Sperm Analysis (CASA). Sperm characteristics have also been studied comparing monogamous species including humans and the eusocial naked rodent mole using CASA (SCA, Microptic SL, Barcelona, Spain).

It was possible to induce hyperactivation of more than 20% in most species provided sperm quality was high and/or there has been proof of live birth outcome and this relates closely to similar outcomes in humans. Furthermore, the naked rodent mole provided very similar characteristics in terms of sperm morphology to human sperm and even considerably poorer characteristics in terms of sperm motility than for human sperm. It seems that in the absence of sperm competition as evident in humans and naked rodent moles, sperm quality may be controlled/down regulated at much lower levels than when sperm competition is high. This information also provides new insights into the question: 'is human sperm quality in general so bad after all'?

Grzegorz Jakiel, Kornelia Zaręba

VARICOCELE OF THE SPERMATIC CORD

1st Department of Obstetrics and Gynaecology, Postgraduate Medical Education Centre in Warsaw, Poland; e-mail: grzegorz.jakiel1@o2.pl

Varicocele of the spermatic cord, namely abnormal enlargement of the veins, is one of the most common reasons for male infertility. In the great majority of cases this condition is observed on the left. Literature presents numerous theories on its formation – starting from a difference between drainage from the right and left internal spermatic vein, followed by venous valve insufficiency leading to reflux of venous blood followed by an increase in hydrostatic pressure. Varicocele was also observed in men who practised intensive physical activity in the puberty period. Its incidence usually grows with age: from 18% at the age of 30–39 years to 75% at the age of 80–89 years. The main reasons for infertility due to varicocele include the following mechanisms: hypoxia, autoimmune mechanism, oxidative stress and increased testicular temperature. Currently, a theory of oxidative stress has the most followers as this condition leads to ischaemia, temperature stress and increased production of such vasodilators like nitric suboxide. American Society of Reproductive Medicine (ASRM) (2014) recommends treatment of varicocele of the spermatic cord in the following cases: varicocele is observed in a physical examination, a couple meets infertility criteria and a female partner is fertile or her cause of infertility has been treated, and duration of necessary treatment is not a problem, partner's semen has been found to be abnormal. Available treatment options include: open surgery, laparoscopic surgery, microsurgical surgery or embolisation of the vein of the spermatic cord. The highest rate of pregnancies (up to 40%) is observed as a result of microsurgical surgeries. If non obstructive azoospermia had been confirmed in almost 44% of patients after surgery for varicocele of the spermatic cord sperm cells were observed in the ejaculate. The spontaneous pregnancy rate was 13.6%. The mean time to a spontaneous pregnancy was 12.7 months (6-25 months) (*Esteves et al.*: Asian J Androl., 2016, 18, 246–253).

Sławomir Jakima

DELAYED EJACULATION – DIFFICULT CLINICAL PROBLEM

Outpatient Clinic of Sexology and Sexual Pathology, Warsaw; e-mail: s.jakima@wp.pl

Delayed ejaculation (DE) is one of the most difficult and complex clinical problem, beginning with the establishment of the diagnosis to the therapeutic conception. There are various diagnostic ideas with the lack of the clear algorithm of the procedure. DE is a very rare disease, with the occurrence rate around 1–4% of the men population (*Chen*: Transl Androl Urol, 2016, 5, 549–562). The basic symptoms are the ability to achieve ejaculations and orgasms within varied sexual situations besides ejaculation in the partner's vagina. There are few therapeutic options for the disease - pharmacologic treatment, behavioural training and psychotherapy (*Abdel-Hamid et al.*: Transl Androl Urol 2016, 5, 576–591). The most probable etiologic factors of the disorder are psychologic and relational problems/difficulties.

DE treatment options are presented (*Lawrance et al.*: Fertil Steril, 2015, 104, 1082–1088).

Joanna Jakubik[1], Kamil Gill[1], Aleksandra Rosiak[1,5], Michał Kupś[4,5], Łukasz Patorski[1,3], Rafał Kurzawa[2,5], Monika Frączek[6], Maciej Kurpisz[6], Małgorzata Piasecka[1]

ASSOCIATION BETWEEN STANDARD SEMEN PARAMETERS AND SPERM CHROMATIN MATURITY

[1]Department of Histology and Developmental Biology; [2]Department of Procreative Health, Pomeranian Medical University in Szczecin; [3]Department of Gynecology, Endocrinology and Gynecological Oncology, SPSK1, Pomeranian Medical University in Szczecin; 4Department of Urology an Oncological Urology, Regional Specialist Hospital in Szczecin; 5VitroLive Fertility Clinic in Szczecin, Poland, 6Institute of Human Genetics in Poznan, Polish Academy of Sciences; email: jakubik_joanna@wp.pl

There is a need to search for molecular biomarkers for spermatozoa, because the standard semen analysis is not a sufficient tool to reveal sperm quality changes (*Fernandez-Escinas et al.*: J Urol. 2016, 195, 213–219). Therefore, we have decided to investigate the relationship between conventional sperm characteristics and the maturity of their chromatin using complementary tests.

Men with abnormal standard semen parameters had a significantly higher proportion of spermatozoa with reduced protamination (chromomycin A3 test – CMA3), increased number of residual histones (aniline blue test – AB), abnormal chromatin condensation (toluidine blue – TB test), single DNA strands (acridine orange test - AO) and fragmented genetic material (HaloSperm test) as compared to men with normal sperm parameters. Similar results were obtained for men with oligozoospermia, astenozoospermia, and teratozoospermia as compared to men with normal sperm numbers in ejaculate, their motility and morphology. Sperm DNA fragmentation positively correlated with male age, teratozoospermic index, number of spermatogenic line cells and leucocyte concentration in ejaculate, as well as negatively with number of sperm concentration, morphology, motility and vitality. In addition, AB scores positively correlated with CMA3, TB, and HaloSperm tests. Moreover, HaloSperm assay results positively correlated with the TUNEL test findings.

The results indicate that abnormal standard semen parameters may be associated with molecular abnormalities of sperm chromatin which are most likely results from developmental failure in the spermatogenic remodelling process, since abnormal number of nuclear histones coexisted with DNA fragmentation, reduced protamination and DNA condensation. Supplementation of conventional sperm characteristics seems necessary.

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Piotr Jędrzejczak

MALE REPRODUCTION IN THE 21ST CENTURY NEW CHALLENGES

Clinic of Infertility and Reproductive Endocrinology, Medical University of Poznan, Poland; e-mail: piotrjedrzejczak@gmail.com

The colonization of new planets, work in space are undoubtedly goals that light up the imagination of many people. An interesting issue is certainly the impact of space travel on human reproduction.

Potential threats to human life are certainly microgravity, cosmic rays, and the stress of space missions. The lecture will discuss the current state of knowledge about the impact of space travel on the male reproductive system and the prospects for the future research.

Marzena Kamieniczna[1], Agnieszka Malcher[1], Anna Havrylyuk[2], Andrij Nakonechnyj[3], Justyna Rajewska[4], Marek Rybkiewicz[4], Natalia Rozwadowska[1], Monika Frączek[1], Elżbieta Gawrych[4], Valentina Chopyak[2], Maciej Kurpisz[1]

ANDROGEN RECEPTOR GENE CAG AND GGN REPEATS LENGTH IN PREPUBERTAL BOYS WITH CRYPTORCHIDISM AND MEN FROM UKRAINE AND POLAND

[1]Institute of Human Genetics in Poznan, Polish Academy of Sciences; [2]Danylo Halytsky National Medical University, Department of Clinical Immunology and Allergology, Lviv, Ukraine; [3]Danylo Halytsky Lviv National Medical University, Department of Pediatric Surgery, Lviv, Ukraine; [4]Department of Pediatric and Oncological Surgery Pomeranian Medical University, Szczecin, Poland; e-mail: marzena.kamieniczna@igcz.poznan.pl

Cryptorchidism is the most frequently urogenital pathology in prepubertal boys with impaired reproductive function in the adults. The increased incidence of cryptorchidism has been observed. The genetic background seems to be important. Altered genetic background seems to be most likely causing CAG and GGN repeats number in androgen receptor (AR) gene.

The aim of study was to investigate CAG and GGN polymorphism distribution in populations of prepubertal boys with cryptorchidism (n = 44, both gonads defect n = 20) and in population of healthy Ukrainian men (n = 30). The another studied control groups were: non-selected group of healthy men from two regions of Poland (Great Poland n = 113, Lublin Region n = 89), healthy fertile (n = 90) and infertile (n = 40) men from Poland.

Materials and methods: DNA extraction from peripheral blood samples (EDTA) was performed using salting out technique (6M NaCl). Polymerase chain reaction (PCR) of the AR gene with primers specific for repeats CAG and GGN was carried out. Strands were directly sequenced and the length was calculated by using AB Hitachi 3130xl Genetic Analyser, (Applied Biosystems).

Results: In prepubertal boys with cryptorchidism the mean CAG repeat length was 22,0 (16–30), and GGN 23,2 (19–27) and did not differ significantly from the group of control healthy men. In the group of healthy men (Ukrainian population) the mean CAG repeat length was 22,8 (17–28), and the mean GGN repeat length was 22,4 (16–24) and did not differ from that in the other West-European populations. Similar results were found in non-selected groups of healthy men in Poland: CAG (22,02 ±2,82) and GGN (23,29 ±1,59).

The study was financed by the National Science Center (grants No. 2012/05/N/NZ5/00893 and 2015/19/B/NZ5/02241).

Alicja Kamińska, Sylwia Marek, Laura Pardyak, Małgorzata Kotula-Balak, Barbara Bilińska, Anna Hejmej

EFFECTS OF ENDOCRINE DISRUPTING CHEMICALS ON NOTCH SIGNALING PATHWAY IN RAT TESTIS

Department of Endocrinology, Institute of Zoology and Biomedical Research, Jagiellonian University in Krakow, Krakow, Poland; e-mail: ala.kaminska@doctoral.uj.edu.pl

Bisphenol A (BPA) and dibutyl-phthalate (DBP) are plastic derived compounds that accumulate in the environment and can negatively impact on endocrine system and male reproductive functions in mammals. Both BPA and DBP are classified as endocrine disrupting chemicals and their effects on testicular functions are mostly assigned to their estrogenic and anti-androgenic actions. Other mechanisms have been also proposed to explain disturbed testis development and function by plastic derived compounds, including alterations in gap junctional communication between testicular cells. A question arises as to whether another type of direct intercellular communication in the testis – juxtacrine signaling – may be a target for BPA and DBP. The Notch signaling pathway involved in juxtacrine communication is an important regulator of proliferation and differentiation in several tissues, including testis.

Present study was designed to explore the effects of BPA and DBP treatment on the expression of Notch signaling components: Notch1 receptor, Dll4 ligand and the effector genes Hes1, Hes5 and Hey1 in adult rat testis.

The study was performed on testis explants isolated from adult Wistar rats and cultured in vitro. Based on the results of dose-response experiment explants were treated with BPA (5×10^{-6}M, $2{,}5 \times 10^{-5}$M, 5×10^{-5}M), DBP (10^{-6}M, 10^{-5}M, 10^{-4}M) or a vehicle (0,01% DMSO) for 24 h. Real-time RT-PCR and semi-quantitative western blot (WB) were used for the analyses of Notch1, Dll-4, Hes1, Hes5 and Hey1 expressions at mRNA and the protein level, respectively. The localization of the proteins was analyzed using immunohistochemistry.

Real-time RT-PCR and WB analyses revealed upregulation of Notch1 and Dll4 at the mRNA and protein level in the testis explants after BPA and DBP when compared to the control. Detailed analysis revealed enhanced immunoreactivity of activated Notch1 in Sertoli cells of DBP-exposed seminiferous tubules. Signal intensity of Dll4 in germ cells was enhanced following the exposure to both BPA and DBP. Increased Notch1 and Dll4 immunoexpression was also detected in the interstitial tissue of treated explants.

As a result of Notch signaling activation following BPA and DBP exposures, Hey1 mRNA and protein was significantly upregulated. Hes1 expression was affected neither by BPA nor DBP exposure, while Hes5 was downregulated only by BPA.

Taken together, our data provide evidence that BPA and DBP affect Notch signaling in both seminiferous epithelium and interstitial tissue which indicates an adverse effect of these chemicals on juxtacrine communication in the male gonad. This may be considered as a novel mechanism mediating impairment of testicular functions following exposure to endocrine disrupting chemicals.

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George Kanakis[1]*, Stamatina Nicopoulou*[2]

TREATMENT OF OLIGOZOOSPERMIA

[1]Athens Naval and Veterans Hospital; [2]Elena Venizelou Maternity Hospital of Athens, Athens, Greece; e-mail: geokan@endo.gr

Oligozoospermia refers to reduced sperm density and is often accompanied by defects in sperm motility and

morphology (oligo-astheno-terato-zoospermia), reflecting both qualitative and quantitative aberrations of spermatogenesis. An estimated 15% of couples of reproductive age fail to achieve pregnancy within a 12-month period and in almost 50% a male infertility (MI) factor is implicated (*Jungwirth et al.*: Eur Urol., 2012, 62, 2, 324–332). Oligozoospermia may occur as a result of several reproductive or systemic disorders; however, in up to 75% of cases a cause cannot be identified (idiopathic oligozoospermia; IO) (*Punab et al.*, 2017). The role of the Andrologist is to identify possible treatable causes of MI, which with proper treatment may allow natural conception or to determine those couples that can benefit from Assisted Reproduction Treatment (ART) and suggest the preferable method.

Hypogonadotropic hypogonadism is a cause of MI that can be treated successfully with the administration of gonadotropins in almost 80% of cases (*Liu et al.*: J Sex Med., 2009, 6, 4, 936–946)SETTING, AND PARTICIPANTS A total of 75 men, with 72 desiring fertility, was treated at two academic andrology centers for a total of 116 courses of therapy from 1981-2008. OUTCOMES Semen analysis and testicular examination were performed every 3 months. RESULTS A total of 38 men became fathers, including five through assisted reproduction. The median time to achieve first sperm was 7.1 months [95% confidence interval (CI. Similarly, surgical or medical treatment of a tumor of the sellar region might re-install fertility. Regarding IO, most of suggested therapies are empirical and supported by weak evidence (*Dabaja* and *Schlegel*: Transl Androl Urol., 2014, 3, 1, 9–16). It should be stressed that testosterone despite of being essential for spermatogenesis, when administered exogenously suppresses the reproductive axis and should be avoided. Aromatase Inhibitors and Selective Estrogen Receptor Modulators have both been used in IO, in an attempt to hyper-stimulate spermatogenesis and sperm maturation (*Koukkou et al.*: Andrologia, 2012, 44, 5, 337–342)testosterone undecanoate (40 mg t.i.d., whereas the role of FSH treatment has been recently re-evaluated with promising but preliminary results (*Santi et al.*: Endocr Connect., 2015, 4, 3, R46–58). Modern lifestyle (obesity, smoking, pollutants) has also been associated with MI, including IO, attributing a central role to elevated oxidative stress. Adoption of a healthy lifestyle should be encouraged to assist fertility and for general health *(McLachlan*: Clin Endocrinol (Oxf)., 2013, 78, 2, 176–180); however prescription of vitamins and antioxidants for improving IO is supported by weak evidence (*Showell et al.*: Cochrane Database Syst Rev., 2014, 12, CD007411). Varicocele (VC) is a common finding in IO, however a causative role is debated. Moreover, the efficacy of surgical repair of VC in the treatment of infertility is not universally accepted and should be reserved for selected patients with clinically evident VC and sperm defects (*Evers et al.*: Cochrane Database Syst Rev., 2009, 1, CD000479).

ART and especially ICSI is a revolutionary method that has offered fatherhood to men with otherwise untreatable infertility. Despite of not being an etiological therapy, it should not be delayed in cases of IO, particularly in cases of advanced age of the female partner, the major predictor of success (*Creus et al.*: Hum Reprod. 2000, 15, 11, 2341–2346). Nevertheless, etiology of MI should still be extensively sought as it may provide information for associated comorbidities (e.g. testicular cancer). In cases of severe oligozoospermia not otherwise explained, possible underlying genetic defects (chromosomal anomalies, Yq-microdeletions) that may impact the success of ART and offspring safety should be excluded (*McLachlan*: J Clin Endocrinol Metab., 2010, 95, 3, 1013–1024).

Agnieszka Kolasa-Wołosiuk

DISTURBED ANDROGENIC HOMEOSTASIS CAUSED BY FINASTERIDE AND ITS INFLUENCE ON TESTIS AND EPIDIDYMIS MORPHOLOGY AND PHYSIOLOGY OF MALE WISTAR RATS AND THEIR PROGENY

Pomeranian Medical University in Szczecin, Chair and Department of Histology and Embryology, Poland;
e-mail: agnieszka.kolasa@pum.edu.pl

A reduction in the semen quality and increasing problems regarding male fertility may be caused by, *inter alia*, lifestyle-related etiological factors, exposure to radiation, environmental factors with hormonal activity, and also certain medications. One of them could be finasteride, used in the treatment of prostate cancer and benign prostatic hyperplasia as well androgenetic alopecia of young men. It used to be widely believed that chronic therapy did not have a negative effect on fertility or libido however, nowadays the terms '*finasteride sexual side effects*' and '*no pregnancy result'* are commonly used (*Fertig et al.*: Am J Mens Health., 2015, 9, 222–228). The spermatozoa collected from the patients had higher sperm DNA fragmentation index, more frequent microdeletions on the Y chromosome and elevated diploidy and sex chromosome disomy frequencies, which did not decrease after one year of drug interruption, despite of the improved morphology and sperm motility (Şalvarci *et al.*: Int Urol Nephrol., 2013, 45, 83–85; *Tu* and *Zini*: Fertil Steril., 2011, 95, 2125.e13–4, *Collodel et al.*: Arch Androl., 2007, 53, 229–233). Finasteride, similar to many other endocrine disruptors, that change the T to DHT ratio, can be considered to be one of the reprotoxicants. Prenatal finasteride exposures of rats and rhesus macaque monkeys resulted in changed anogenital distance, nipple retention, lack of prostate, ectopic testes, small scrotum and penis, hypospadias (*Prahalada et al.*: Teratology, 1997, 55, 119–131; *Bowman et al.*: Toxicol Sci., 2003, 74, 393–406). Furthermore, the results of my research on mature male rats of the F0 generation after exposure to finasteride

indicated abnormal morphology of the seminiferous epithelium, premature release of immature germinal cells, abnormalities in the expression of cell junction proteins, and changes in the pattern of expression of the antioxidant enzymes in the epididymis. Therefore, next aim of my research was to determine whether the administration of finasteride to paternal males could have a negative effect on the reproductive system in the male offspring (F1:Fin). Beyond the difficulty in raising male offspring (small litter size, elimination of the young by females, *sex ratio* shift towards females), my results showed that the exposure of mature males to finasteride induced a transgenerational effect that was revealed in male F1:Fin offspring as a change of: 1) levels of serum and intratesticular T and DHT, 2) intercellular communication, which may cause abnormalities in spermatogenesis, 3) protective, antioxidant function of the epididymis, that may impair the process of epididymal sperm maturation.

Małgorzata Kotwicka[1], *Izabela Skibińska*[1], *Piotr Jędrzejczak*[2]

EXPRESSION OF PELP1 PROTEIN IN SPERMATOZOA OF MEN DIAGNOSED DUE TO INFERTILITY

[1]Department of Cell Biology; [2]Division of Infertility and Reproductive Endocrinology, Poznan University of Medical Sciences, Poznan, Poland; e-mail: mkotwic@ump.edu.pl

It is indicated that human spematozoa might be target cells for estrogens. Estrogens act on target cells via estrogen receptor type 1 (ESR1) and type 2 (ESR2), both of which are present in human sperm cells. It is assumed that up to 5–10% of all cells' ESRs have membrane localization. Structure of classical ESRs does not contain transmembrane domains that are characteristic for membrane receptors. Because of that fact it is suggested that ESRs are only anchored in the cell membrane or are bound to other membrane proteins. Both types of ESRs do not show kinase activity, so additional proteins have to be involved in the ligand-receptor signal transduction pathway. Proline leucine glutamic acid rich protein 1 (PELP1), is considered to be the ESR signal transduction coordinator, as it has the ability to bind both, ESR1 and ESR2. In non-genomic signaling, PELP1 mediates signal transduction between ESR and cytoplasm by conjugating ESR with the kinases present in the cytosol. Interactions between ESR and PELP1 occur via the LXXLL motifs and the estrogen receptor AF2 fragment. PELP1 also binds to several other receptors, such as the androgen receptor, glucocorticoid or progesterone receptors. This protein also interacts with growth factor receptors.

Our research has demonstrated the presence of PELP1 in the nuclei of the spermatogenic cells as well as in the posterior part of heads and in the midpieces of the mature spermatozoa. The expression level of PELP1 was significantly higher in spermatozoa of men with pathological semen parameters. Statistically significant negative correlation was found between the sperm expression of PELP1, the concentration, total number of spermatozoa and their motility, morphology and viability.

Rafał Kubiak

THE PATIENT'S RIGHT TO PRIVACY AND RESPECT FOR DIGNITY

Department of Criminal Law, University of Lodz; Department of Medical Law, Medical University of Lodz, Lodz, Poland; e-mail: rafal.kubiak@umed.lodz.pl

In modern democratic countries humanistic values are strongly emphasized. It is directed to treat the human subjectively and respect their individualism. Privacy and human dignity are therefore considered to be valuable goods. The justification of their respect may be sought both in the psychological and social concepts. These values are therefore also strongly protected under the law. Their vital importance is also indicated by the fact that they have been raised to the constitutional level and are the subject of protection in both civil and criminal provisions. Plenty of space is devoted to this subject in medical law as well. While providing health benefits, frequent violation of these values may in fact occur. This announcement is to present the theoretical foundations of the right to privacy and dignity of the patient, sources of legal regulation as well as ethical and deontological grounds concerning this matter and to provide examples of violations of these goods. A situation of privacy may lead to its violation in a physical sense (e.g.: due to the body exposure), as well as in intellectual terms (through disclosure of intimate data - such as medical procedures performed). This announcement will also discuss the legal admissibility of the participation of strangers during medical procedures (including so-called close persons, a person designated by the patient, medical personnel and trainees in medical professions). In particular, an analysis of the principles of granting consent for the participation of such persons in the performance of health services for children as well as incapacitated, decrepit and unconscious persons is going to be made.

Respect of dignity is based on a subjective treatment of the patient as an equal human being. This announcement is going to present the proper way of dealing with the patient, so as not to violate their dignity in both the intellectual and physical activities. The last part of this announcement is going to present the legal consequences that may occur in the event of violations of the right to privacy and respect of dignity. Doing so may justify pursue of civil claims, mainly due to the violation of personal interest. Some of such behaviour infringing discussed goods can deplete the attributes of a prohibited act, especially against honor and bodily inviolability, as

well as lead to criminal liability for disclosure of physician's medical secret. Moreover, violation of presented value may be treated as professional misconduct and justify responsibility before a medical court.

Maria Laszczyńska[1], *Aleksandra Rył*[1], *Katarzyna Grzesiak*[1], *Weronika Ratajczak*[1], *Kinga Walczakiewicz*[1]

PROSTATIC HYPERPLASIA – EXPERIMENTAL AND CLINICAL STUDIES

Department of Histology and Developmental Biology, Pomeranian Medical University in Szczecin, Poland; e-mail: maria@laszczynska.pl

Benign prostatic hyperplasia (BPH) is one of the most common diseases observed in aging men. Histopathological changes in the prostate gland may affect as many as half of men over 50 years of age, and this percentage increases by approximately 10% after every decade of life. Analysis of the society structure and demographic forecasts shows that the number of men with this health problem will grow. BPH is easier to diagnose than prostate gland tumors. As early as during the first stages of its development, BPH can cause symptoms associated with the urinary tract function. Its pathophysiology has not so far been thoroughly elucidated. We know that there are many – both modifiable and non-modifiable – risk factors, contributing to this disease. The main of them are age, metabolic syndrome, obesity, diabetes, hypertension, and bad dietary habits. The prevalence of BPH, problems with its treatment, and desire to know more about its pathophysiology, result in experimental and clinical studies concerning a number of BPH-related issues (*Chughtai et al.*: Nature Reviews Disease Primers, 2016, doi: 10.1038/nrdp.2016.31). Some researchers conduct such studies on rat models to assess the potential of antioxidants szczurów (*Chen* and *Song*: Environ Toxicol Pharmacol., 2016, 45, 315–320; *Kim et al.*: J Med Food., 2016, 19, 746-752) and new pharmaceuticals to stop the development of BPH (*Chen et al.* J Huazhong Univ Sci Technolog Med Sci., 2016, 36, 806-810). Others search for new mechanisms in the etiopathology of BPH, and indicate the role of the parasympathetic nervous system and autophagy in the occurrence of this disease (*Cai et al.*: Chin Med J (Engl)., 2017, 130, 1953-1960). Clinical studies of BPH patients, on the other hand, provide analysis of the mechanisms underlying molecular pathogenesis of prostatic hyperplasia, thus giving the possibility of looking for new and patient-tailored therapies for prostatic hyperplasia (*Henry et al.*: Prostate, 2017, 77, 1344-1355). There are also numerous reports on the influence of inflammation and inflammatory factors on the BPH onset and etiopathology (*Xu et al.*: Eur J Histochem., 2017, doi: 104081/ejh. 2017.2775). Exploration of the BPH problem on so many fields allows for learning more about its causes, and creates an opportunity to seek new therapeutic goals.

Małgorzata Piasecka[1], *Kamil Gill*[1], *Aleksandra Rosiak*[1,4], *Joanna Jakubik*[1], *Łukasz Patorski*[1,3], *Mariola Marchlewicz*[2]

FROM MORPHOLOGICAL TO MOLECULAR STUDIES OF SPERMATOZOA

[1]Department of Histology and Developmental Biology; [2]Department of Aesthetic Dermatology, Pomeranian Medical University in Szczecin; [3]Department of Gynecology, Endocrinology and Gynecological Oncology, SPSK1, Pomeranian Medical University in Szczecin; [4]VitroLive Fertility Clinic in Szczecin, Poland; e-mail: mpiasecka@ipartner.com.pl

The increasing importance of the male factor in couple infertility has resulted in the dynamic development of diagnostic assays beyond the standard semen analysis, which is the primary tool for verifying sperm abnormalities but which in many cases has insufficient value in predicting a sperm cell's ability to fertilize an oocyte in terms of spontaneous conception as well as medically assisted. Thus, the introduction of complementary research methods has become justified and inevitable for andrological laboratories, especially when dealing with idiopathic infertility, where molecular biomarkers should be sought (*Tashmaspour et al.*: J Assist Reprod Genet., 2014, 31, 1115–1137).

There is no doubt that sperm structural disorders already visible in light microscopy (especially advanced ones) or just emerging in electron microscopy (transmission and scanning) and causing numerous functional abnormalities of male gametes may be related to their molecular defects, including genetic abnormalities (eg. point mutations and translocations of chromosomes, autosomal and sex chromosome disomy) and consequently may be the cause of unexplained recurrent spontaneous abortions (*Cao et al.*: Ontotarget. published online 19.04.2017; *Collodel et al.*: Andrologia, 2009, 41, 352–360; *Nussdorfer et al.*: Bosnian J Basic Med Scien. published online 18.06.2017).

It has been shown that macrocephaly, crater defect and globozoospermia (mutation of the genes *SPATA16*, *PICK1* and *DPY19L2*, *AURKC* genes) have genetic background (*Gatimel et al.*: Andrology, 2017, 5, 845–862). In turn, spermatozoa with a detached tail defect or without head (acephalic, decapitated sperm syndrome, pinhead sperm) are accompanied by mutations in the *BRDT* and *SUN5* gene, diploidy of chromosome 18, X and Y and chromatin condensation disorders (*Li et al.*: Oncotarget, 2017, 8, 19914–19922). Mutations in the *AKAP3*, *AKAP4*, *DNAH1* and *GAPDS* genes as well as chromosome X and Y disomy are found in the dysplasia of the sperm fibrous sheath manifested in the semen the presence of short, thick, sometimes stump tails (*Baccetti et al.*: Hum Reprod 2005, 20, 2790–2794). Furthermore, mutations in *DNAH1* (28% of cases), *CFAP43* and *CFAP44* genes and increase the percentage of aneuploidy and sperm DNA fragmentation are discovered in case of multiple morphological abnormalities of the sperm flagella (MMAF) demonstrated by wrapped, bent, short sperm tail or the

lack of it (*Coutton et al*.: Hum Reprod Update 2015, 21, 4554–85; *Ray et al*.: Clin Genet 2017, 91, 217–232; *Tang et al*.: Am J Hum Genet, 2017, 100, 854–864; *Wambergue et al*.: Hum Reprod., 2016, 31, 1164–1172).

In the described anomalies, the use of *in vitro* fertilization procedure carries the risk of passing of molecular defects to next generations. Mostly, however, it may end with a lack of reproductive success. Hence, the selection of patients (men with curable and incurable infertility) becomes necessary because it allows for proper therapeutic treatment.

Lechosław T. Putowski, Joanna Tkaczuk-Włach

HOW TO BE A FATHER IN THE WORLD OF STIMULANTS AND DRUGS?

Department of Gynecology and Gynecological Endocrinology, Military Clinical Hospital, Medical University in Lublin, Poland; e-mail: putowskil@yahoo.com

As a result of the evolution process, a specific way of extending species has developed over millions of years. However it is difficult, to point out another species, apart from the man himself contributing to the natural disruption of the life cycle of the process. Examples of this type of activity are continuous exposure of the body to harmful environmental factors, including increased use of commonly used substances known as stimulants or drugs. These factors are detrimental to the reproductive system in both sexes. Forming sperm are exposed to damage throughout the life of the men, due to the continuous development of new reproductive cells in the process of spermatogenesis. This can lead to sperm DNA damage, gonadal cell apoptosis, periodic or complete inhibition of spermatogenesis and sperm maturation. However, due to the complex design of the study, it is difficult to talk about obtaining some results on a representative group of individuals. At the same time, a number of chemicals have been identified, which have been proven to have a detrimental effect on male fertility beyond all doubt. The best known adverse chemical agent is tobacco smoke. The substances contained in it increase the number of free radicals, which in turn leads to increased peroxidation of unsaturated fatty acids in the cell membrane and the loss of sperm motility. Free radicals can also damage the integrity of sperm DNA and the mitochondria present in them. This can also affect the sperm motility. Another well-known substance that stimulates the formation of free radicals is ethanol. Excessive consumption of alcohol leads to a decrease in the antioxidant capacity of the body and to hypothalamic-pituitary-gonadal dysfunction, which in turn can lead to a decrease in serum testosterone. Testosterone plays an important role in the development and maintenance of male reproductive function, but exogenous androgens, anabolic steroids as used by some athletes, may have a negative impact. Excess levels of testosterone can suppress gonadotropins, which in turn reduces the production of endogenous testosterone in the testes and consequently reduces spermatogenesis. The result may be testicular atrophy, decreased testosterone levels and reduce fertility. These changes may also be responsible for the increased incidence of sex chromosome aneuploidy in offspring. Increased testosterone levels and anabolic androgenic steroids (AASs) may impair the functioning of the hypothalamic-pituitary-gonadal axis by inhibiting the hypothalamus and the pituitary gland. This in turn can reduce the concentration of luteinizing hormone leading to inhibition of testosterone production, and consequently inhibit spermatogenesis. In addition to reduced sperm counts, reduced volume of testicles in some people taking AASs are observed other symptoms of hypogonadism such as decreased libido and erectile dysfunction. Back to normal parameters for people using AASs is possible, but it may take a relatively long time.

Testis are also the place of action of the endocannabinoid system present in seminal plasma, sperm and epididymis. This system is involved in the regulation of sperm motility, capacitation, acrosomal reaction, and thus in the regulation of fertility. It becomes evident that exogenous cannabinoids, such as marijuana and opiates, may interfere with male fertility by inhibiting gonadotropin secretion, mainly LH, and cause a decrease in testosterone production in the testis. In addition, prolonged use of opioids may cause idiopathic effects and increase serum prolactin levels. Using marijuana can also cause other disorders such as problems with an erection. Cocaine is a stimulant of central nervous system activity and may also inhibit LH release and prolactin release from the pituitary gland. However, there are no studies showing the effect of cocaine on male fertility, however, suggesting adverse effects of the drug on the quality of the sperm.

There is no doubt that the use of substances in the group of drugs can cause male fertility disorder. Their harmful effect is dependent the length of their use, dose levels, and individual sensitivity of the body. It is also certain that avoiding harmful substances can prevent potential problems with male fertility. The proposed therapy should be adapted to the cause of the changes, although its efficacy is always questionable.

Ewa Rajpert-De Meyts

CONTRALATERAL TESTIS BIOPSY IN PATIENTS WITH TESTICULAR GERM CELL CANCER: SHOULD IT BE PERFORMED ROUTINELY?

Department of Growth and Reproduction, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark, e-mail: erm@rh.dk

Testicular germ cell tumours (TGCT) of young adults (seminoma or nonseminoma) develop from a preinvasive stage of germ cell neoplasia *in situ* (GCNIS), previously

known as carcinoma *in situ* (CIS) testis (*Rajpert-De Meyts et al.*: Lancet, 2016, 387, 1762–1774; *Ulbright et al.*: WHO Classification 2016). Patients with a unilateral TGCT are at increased risk of harbouring GCNIS in the contralateral testicle and of developing a second metachronous tumour. As a preventive measure, a surgical biopsy of the contralateral testicle taken simultaneously with orchiectomy has been routinely performed since mid-1980s in Denmark (*Berthelsen et al.*: Br Med J 1979, 2, 363–364). This was later followed in other countries, especially in Northern Germany, where two-site biopsies were advocated to increase sensitivity (*Dieckmann et al.*: Eur Urol., 2007, 51, 175–185; *Ruf et al.*: Andrology 2015, 3, 92–98). However there has been ongoing controversy concerning usefulness of the procedure among urologists and oncologists. A recent nation-wide retrospective analysis in Denmark revealed that that 1.9% patients in the screened cohort developed a metachronous TGCT within a follow-up of period of 20 years, which was mainly due to false-negative biopsies (*Kier et al.*: Annals Oncol 2015, 26, 737–742). This prompted us to perform a separate analysis of our data from an 11-year-long period (1996–2007), during which biopsies from 659 patients were evaluated according to a standardised protocol with immunohistochemical (IHC) staining for GCNIS markers. In 7% patients, GCNIS was identified and treated, and this rate was significantly higher than 4% nationwide. At the median follow-up period of 12 years (min. 10 years, max 21 years), only 5 (0.76%) patients developed a metachronous TGCT in our centre, significantly fewer than 2.2% of non-biopsied TGCT patients from an earlier period (*Rajpert-De Meyts et al.*, in preparation).

In conclusion, screening for GCNIS in the contralateral biopsy prevents the occurrence of second malignant TGCT in a 4–7% of patients. Care must be taken to perform biopsies in specialised centres, according to high technical standards, with a good size biopsy and mandatory IHC. However, even the best currently available protocol of contralateral biopsy was not able to prevent all cases of metachronous TGCT, calling for more research for development of new, more sensitive methods of screening.

Andrzej Rogoza, Marta Pietruszczak

CASE OF BIOCHEMICAL PREGNANCY AFTER IVF-ICSI PROCEDURE WITH SEMEN FROM MAN WITH KARTAGENER SYNDROME

Infertility Treatment Clinic INVIMED, Gdynia, Poland; e-mail: rogoza@poczta.fm

Kartagener's syndrome is rare autosomal recessive genetic disorders (*Berdon and Willi*: Pediatr Radiol, 2004, 34, 1, 38–42). It is characterized by the triad of symptoms like: situs inversus, chronic sinusitis and bronchiectases. The basis of this disorder is a mutation in the gene coding dyneine protein in cilia (*Chilvers et al.:* J Allergy Clin Immunol, 2003, 112, 3, 518–524). The consequence of this mutation is asthenzoospermia. In order to achieve pregnancy in *in-vitro* procedure it was developed few methods to select (activate) proper sperm able to fertilize oocyte by intracytoplasmatic sperm injection (ICSI) e.g. pipette method, pentoxifiline actiavetd sperm (*Cayan et al.:* Fertil Steril, 2001, 76, 3, 612–614; *Hattori et al.*: Fertil Steril. 2011, 95, 7, 2431.e9–11).

A 28-years-old men with Kartagener's syndrome, with body mass index (BMI) 30,2 kg/m^2, with normal testicular and penis anatomy, in spermiogram had sperm concentration 36 mln/ml, immotile sperm, vitality (Host-test) – 63% and normal morphology – 4%. The female partner was stimulated by short protocol with gonadoliberin antagonist. We got 8 mature oocytes. Sperms were selected by two methods: pipette and activation by pentoxifiline. We achieve four fertilized oocytes (three with sperms selected by the pipette method and one by the pentoxifiline activation). As a result of the embryo culture two good quality embryos for transfer procedure were received. After 14 days the biochemical pregnancy was confirmed.

Effectiveness of those methods to find out living sperms in Kartagener's syndrome was confirmed. Those methods led to the development of embryos in 3-day-culture. Taking into account that more fertilized oocytes were derived by the pipette method it should be considered that this method may be useful for future cases.

Aleksandra Rosiak[1,6], Kamil Gill[1], Joanna Jakubik[1], Monika Frączek[5], Michał Kups[4,6], Łukasz Patorski[1,3], Rafał Kurzawa[2,6], Maciej Kurpisz[5], Małgorzata Piasecka[1]

SELECTED SEMINOLOGICAL PARAMETERS OF MEN IN DIFFERENT AGE GROUPS

[1]Department of Histology and Developmental Biology; [2]Department of Procreative Health, Pomeranian Medical University in Szczecin; [3]Department of Gynecology, Endocrinology and Gynecological Oncology, Pomeranian Medical University in Szczecin; [4]Department of Urology an Oncological Urology, Regional Specialist Hospital in Szczecin; [5]Institute of Human Genetics in Poznan, Polish Academy of Sciences; [6]VitroLive Fertility Clinic in Szczecin, Poland; e-mail: rosiak.aleksandra@yahoo.com

Late fatherhood becomes a sociological phenomenon. Young people invest in themselves, want to develop themselves, archive proper economic status consequently delay parenthood to fourth, even fifth decades of they live, especially in men case (*Herati et al.*: Fertil Steril 2017, 107, 319–323). The study was designed to evaluate the effect of age on standard (analysis according to WHO, 2010) and molecular (with use aniline blue, toluidine blue, chromomycin A3 and TUNEL tests) semen parameters.

The men ≥40 y had lower ejaculate volume, percentage of sperm with normal morphology and higher proportion of sperm cells with fragmented DNA compared to

men < 40 y. Similar results were obtained in group of men ≥40 y with normal or abnormal semen parameters. They had lower ejaculate volume and higher percentage of male gametes with DNA strand breaks. Men ≥45 y had significantly lower ejaculate volume and total sperm concentration. Furthermore, we found decreasing sperm concentration and increasing teratozoospermic index in group of men between 30–35 y compared to men <30 y. Moreover, men <30y had significantly higher percentage of spermatozoa with normal morphology and motility. The highest ratio of male gametes with abnormal integrity of DNA were observed in men between 41 and 45 y.

Obtained data suggest that increasing male age can affect spermatogenesis. The most important, adverse changes was found >45 y, even >40 y. It is important to rise the awareness of the population about risk connected to late fatherhood.

Iwona Rotter, Aleksandra Rył, Aleksandra Szylińska

OSTEOPOROSIS IN MEN — FACTS AND MYTHS

Department of Medical Rehabilitation and Clinical Physiotherapy, Pomeranian Medical University in Szczecin, Poland;
e-mail: iwona.rotter@pum.edu.pl

Osteoporosis in men is still an underrated problem. Factors that pose the greatest impact on bone mass are its peak level obtained at the age of twenty, and the speed of losing it. In the majority of men, the loss of bone tissue density begins at forty, but – unlike in women – in men this process is not sudden. Osteoblast activity gradually decreases, and lifespan becomes shorter, leading as a consequence to the intensification of bone resorption. Epidemiological studies indicate that lifelong risk of fractures for 50-year-old men is 13%, and increases to 25% for men at the age of 80. An important part in maintaining proper bone density is played by androgens, and especially testosterone. Age-related hypogonadism observed in some men favors a decline in bone density. The role of estrogens is not negligible, either. Available results show that men with decreased estrogen levels have reduced bone density. According to the guidelines of The Endocrine Society from 2012, all men over 70 should undergo densitometry. As for men between 50 and 69 years of age, densitometry is recommended if there are additional risk factors for fractures (*Głuszko*: Med Prakt., 2016, 5, 52–56). It is also suggested that so called fracture risk calculators (for example, the Fracture Risk Assessment Tool, FRAX) should be used in men with great cautiousness due to possible overdiagnosis of osteoporosis, and thus unnecessary treatment. Aside from calcium supplements and vitamin D3, agents employed in the therapy are bisphosphonates, and in justified cases also teriparatide and denosumab. Additional treatment for men with age-related hypogonadism is testosterone, however its influence on the risk of fractures remains unknown.

Anna Rudnicka, Evdochia Adoamnei, Carrie Nielson, José A. Noguera-Velasco, Jaime Mendiola, Alberto M. Torres-Cantero

ASSOCIATIONS BETWEEN VITAMIN D SERUM LEVELS AND MALE REPRODUCTIVE PARAMETERS

Department of Public Health Sciences, University of Murcia School of Medicine, Espinardo (Murcia), Spain; e-mail: anna.rudnicka@um.es

We have previously reported that semen quality has declined drastically in recent decades. In other populations, low serum vitamin D has been associated with low sperm motility (other parameters?). To assess the association between vitamin D [25(OH)D_{2+3}] serum levels and semen quality and reproductive hormone levels in healthy young men.

Cross-sectional study of 204 male university students (18-23 years old) recruited between 2010 and 2011 in Murcia Region (Spain). All men provided samples for routine semen analysis (semen volume, sperm count, motility and morphology) and blood for measurements of reproductive hormones and total vitamin D [25(OH)D_{2+3}]. Serum total 25(OH)D results were categorized into insufficiency (<50 nmol), sufficiency (50–75 nmol/l), and higher vitamin D status (>75 nmol/l). Relationships between total 25(OH)D categories and semen quality parameters were examined using linear regression, adjusting for BMI, season, age, current smoking status and technical covariates (e.g., abstinence time).

The semen parameters for all men were within normal ranges. Only 2 men (1%) were vitamin D deficient (<25 nmol/l); 18% were insufficient (<50 nmol/l). There were no associations between total 25(OH)D serum levels and any semen parameters (all p >0.15) in crude or adjusted models.

Among young men with normal semen parameters and predominantly sufficient serum 25(OH)D, there was no evidence for an association. It remains to be determined whether low semen quality may be improved by increasing 25(OH)D status. Further investigations are needed in order to confirm and expand these findings.

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Shannen Keyser[1]*, *Liana Maree*[1], *Gerhard van der Horst*[1]

A MODEL TO STUDY POOR AND GOOD SPERM FUNCTIONALITY OF THE SAME PATIENT USING DIFFERENTIAL CENTRIFUGATION AND CASA

[1]Department of Medical Bioscience, University of the Western Cape, South Africa; *e-mail: 3263105@myuwc.ac.za

One in four couples in developing countries is affected by infertility. Male factor infertility is of importance due to

the increase in prevalence and lack of scientific knowledge in the treatment of these patients. Semen analysis is the primary diagnostic test in artificial reproductive technology (ART). Approximately 15% of the presumed cases do not reveal obvious abnormalities, thereby conveying the importance of sperm functional tests. Furthermore, human semen is comprised of a heterogeneous cell population with different degrees of maturation, as well as variation in functional quality and fertilizing ability. Separation of such sperm sub-populations can result in a considerable improvement in the quality of recovered spermatozoa and may provide a model to study good and poor sperm quality of the same patient. The aim of the study was to determine and compare the functional and morphological characteristics of two sperm sub-populations found within the same human semen samples.

Healthy donor semen samples (n = 20) were assessed according to basic semen analysis and further separated into two sub-populations via AllGrad density gradient centrifugation. Both sub-populations of spermatozoa were then used for sperm functional testing, including evaluation of hyperactivation with the use of hyperactivating media (2μm procaine, 5μm caffeine, capacitating media and non-capacitating media), in combination with Computer Aided Sperm Analysis (CASA)(SCA, Microptic SL, Barcelona) measuring sperm motility percentages, sperm kinematics, sperm morphology (SpermBlue® stain), vitality (eosin-nigrosin stain), acrosome reaction induced with calcium-ionophore, presence of reactive oxygen species and mitochondrial membrane potential.

The good sperm fractions were observed to be significantly better than the poor sperm fractions in sperm vitality, acrosome reaction, reactive oxygen species, mitochondrial membrane potential, sperm motility and kinematics and hyperactivation ($p < 0.05$).

These observations assist in our understanding of sperm sub-populations and hopefully the application as diagnostic tools in ART, and further broaden the potential treatment techniques and sperm isolation procedures for infertile men.

Jolanta Słowikowska-Hilczer[1], *Maria Szarras-Czapnik*[2]

FERTILITY IN PATIENTS WITH DISORDERS OF SEX DEVELOPMENT

[1]Department of Andrology and Reproductive Endocrinology, Medical University of Lodz, Lodz; [2]Clinic of Endocrinology and Diabetology, The Children's Memorial Health Institute, Poland;
e-mail: jolanta.slowikowska-hilczer@umed.lodz.pl

Compatibility of genetic, gonadal, genital, somatic and mental sex is required for proper sexual development. If there is no compatibility, disorders of sex development (DSD) appear.

DSD are usually observed in the form of excessive masculinization in people with the female genetic sex, such as congenital adrenal hyperplasia (CAH), or inadequate masculinization in men with the male genetic sex i.e. in testicular dysgenesis, testosterone or dihydrotestosterone biosynthesis disorders or androgen insensitivity. The clinical picture is variable and its severity depends on the patient's age (*Rey et al.*: Best Pract Res Endocrinol Metab., 2011, 25, 221-238).

Medical management in such cases encounters many problems, which largely result from insufficient knowledge of the pathophysiology of these disorders. The main difficulties encountered by the diagnostic and therapeutic team are: determination of gender, anticipation of gender identity, gonadal hormonal function and fertility, as well as the decision to undertake surgical procedures involving genitals and gonads. Therapeutic management is still causing many controversies, among others because people with DSD often have gonads removed due to the high risk of germ cell neoplasia after puberty, thus they are deprived of the chance of having biological offspring.

In the years 2013–2016 European studies dsd-LIFE on the long-term results of surgical and hormonal treatment and psychological support were conducted. The study involved 1040 patients with different causes of DSD. Fertility of these people was investigated among others. It has been shown that most people with DSD are irreversibly infertile (*Slowikowska-Hilczer et al.*: Fertil Steril., 2017, pii:S0015-0282(17)31708-9). However, some DSD do not rule out having children. CAH causes severe hormonal disturbances, which lowers fertility, but with proper hormonal therapy and fertility support, the pregnancy rate in these women is similar to that of healthy women. Infertile are patients with 46, XY and complete androgen insensitivity and complete gonadal dysgenesis, and men with karyotype 46, XX. This is not the case for partial androgen insensitivity or partial gonadal dysgenesis, where fertility maybe possible. In these cases testicular structure may contain spermatogenic cells, and even single spermatozoa in adulthood that can be used for fertilization by the assisted reproductive technologies. Recommendations for therapeutic treatment in people with DSD are developed due to the results of the dsd-LIFE program.

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Jerzy Starzyk

DELAYED PUBERTY IN BOYS

Pediatric and Adolescent Endocrinology Department, Chair of Pediatrics, Medical College, Jagiellonian University, Cracow, Poland;
e-mail: jerzystarzyk@cm-uj.krakow.pl

Transient hypogonadism resulting from Constitutional Delay of Growth and Puberty (CDGP) is the most frequent hypogonadism type in boys. Permanent hypogonadism

caused by either hypothalamo-pituitary impairments (secondary) or by primary testes failure (primary) or by impairment of both these structures simultaneously (combined) appears less frequently. Sexual disorders as well as other non-specific signs may indicate some particular types of hypogonadism. Gonadal dysgenesis is manifested in newborns with disorders of external genitalia development (46,XY DSD) whilst congenital combined pituitary hormone deficiency (CPHD) may manifest with micropenis, microorchidism, cryptorchidism which may by accompanied by hypoglicaemia and hyperbilirubinaemia. Growth inhibition, neurological and ophtalmological signs as well as diabetes insipidus observed in children may be caused by congenital or combined CPHD and are not accompanied by sexual disorders in this period. In adolescents, all disorders leading to hypogonadism are manifested with no increaese in testes volume (>4 mL) at the age of ≥14 years or with no progression of sexual development within the 4.5 year period from the beginning of puberty. The diagnosis of infant hypogonadism is confirmed when the infant is presented with decreased basal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), testosterone, antymüllerian hormone (AMH) and inhibine B. In childhood, hypogonadism is diagnosed on the basis of decreased basal AMH and Inhibin B level. In adolescents, primary hypogonadism is proved by an increased basal level of FSH whilst secondary hypogonadism when LH response after gonadotropin-releasing hormone GnRH stimulation is too low. Low level of inhibine B is typical of combined hypogonadism and may also be useful in differentiation between permanent and transient hypogonadism in CDGP. In secondary hypogonadism magnetic resonance of hypothalamo-pituitary region should be performed whilst in primary hypogonadism, karyotyping and gonad ultrasonography examination are recommended. Surgical treatment is limited to the suprasellar tumors producing local signs, whereas radio- and chemotherapy is the first line therapy in germ cell tumors and optic chiasm glioma. No surgery is recommended in case of tumors caused either by Prop-1 or LHX3 gene mutations. In order to treat micropenis in newborns a few months course treatment with either testosterone or LH and FSH as well as topical dihydrotestosterone is recommended. In secondary hypogonadism the treatment may be started with either recombinant gonadotropins or testosterone.

Piotr Paweł Świniarski

PENILE RECONSTRUCTION AFTER ONCOLOGICAL SURGERY, TRAUMA AMPUTATIONS AND IN INCOMPLETE GENITALIA DEVELOPMENT

St Peter's Andrology Centre and Andrology Department, Institute of Urology, University College London Hospitals, London, United Kingdom; e-mail: piotr.swiniarski@hotmail.com

A normally developed and functioning penis is a very important aspect of male physical and mental well being and health.. Genitalia with congenital abnormalities or acquired abnormalities following oncological treatments or trauma (traffic accidents, intentional injuries) may cause sexual dysfunction, frustration and depression which could result in mental health disorders.

Penile reconstruction may be surgically challenging. The creation of a neophallus should achieve 3 objectives: cosmetically similar appearance to a normal penis, allow the man to engage in sexual intercourse and allow him to void while standing. To gain these goals, the neophallus must have an internal neourethra, and be of sufficient size to allow subsequent placement of a penile prosthesis to allow sexual intercourse. The best effect may be obtained by using skin flaps for penile reconstruction and skin flap or buccal mucosa grafts for urethral reconstruction. Skin flaps may be a rotational flap from the lower abdomen, pubis or groin skin, blood supply then relies vessels from the part of flap not mobilised. Pedicle skin flaps are usually taken from thigh; the blood supply relies on a vessel pedicle. The length and mobility allows transfer of the flap from the thigh to pubis. Free skin flaps are raised from any part of the body, which allows to the surgeon to obtain a sufficient amount of skin with a long vascular bundle. Tubularised skin flaps are sutured to the pubic skin and the neurovascular bundle is microsurgically anastomosed with local arteries, veins and nerves. The flaps most frequently used for penile reconstruction are skin flaps from the lower abdomen, forearm, thigh and latissimus dorsi musculocutanous flap. The final choice depends on the patient's preference, local anatomical circumstances, and surgical experience and preference. A penile prosthesis is usually inserted following recovery from the phalloplasty and resolution of post-operative complication.

Penile reconstruction is a difficult and long procedure with a high risk of complications. However it is feasible and gives a hope for obtaining a fully functional phallus.

Michał Witt

CILIA AND FLAGELLA – BIOLOGICAL DIVERSITY IN GENETIC UNITY

Department of Molecular and Clinical Genetics, Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland; e-mail: michal.witt@igcz.poznan.pl

More than 30 different genes are known to play a role in the primary ciliary dyskinesia (PCD) inheritance. The clinical phenotype of PCD results entirely from the kinetic dysfunction of the cilia. The most important of the PCD genes are genes of outer and inner dynein arms: DNAH5, DNAI1, DNAI2. Radial spokes proteins (RSPH1, RSPH4A, RSPH9) or nexin bridges (CCDC39, CCDC40, CCDC164, CCDC65) are also important. The number of

mutations in individual genes varies in different populations. In the Polish population, *SPAG1* gene mutations are relatively common. Mutations of different genes affect the ciliary structure in a variety of ways. For example, damage to outer dynein arms is caused by 50% mutations in the *DNAH5* gene and 10% by DNAI1 mutations; 10% of outer and inner dynein arms lessions is caused by *SPAG1* mutations; *CCDC40* and *CCDC39* mutations together cause 70% disruption of microtubules with loss of inner dynein arms. Because spermatozoa is an analogous structure to the cellular cilia, similar genetic changes cause flagella defects, affecting their biological functionality.

Jan Karol Wolski

SPERM RETRIEVAL FOR ASSISTED REPRODUCTIVE TECHNOLOGIES

"nOvum" Medical Center; Center of Oncology-Institute Maria Skłodowska-Curie, Department of Urology, Warsaw, Poland; e-mail: jkwolski@op.pl

According to application in treatment of infertility ART (assisted reproductive technologies), mainly IVF (in vitro fertilization), one of the most important tasks of the andrology has become man's generative cell retrieval intended for use in protocols IUI (intrauterine insemination) and IVF. In cases of reduced sperm parameters pharmacotherapy (stimulation of spermatogenesis, the treatment of urogenital infections, immunomodulation) and surgery (operation of varicocele, inguinal hernia, testicular hydrocele, excision of atrophic gonad) can improve the potential of fertility in men. But, aspermia and azoospermia requires operative methods of sperm retrieval. In the case of aejaculation (after spine injury, congenital malformations, abdominal and pelvic surgery neurological disorders, diabetic neuropathy) penile vibrostimulation or electroejaculation are useful methods. In retrograde ejaculation alkalization of urine and bladder catheterization after masturbation can obtains sperm even for IUI. Azoospermia (Non-Obstructive 60% / Obstructive 40%) requires surgical techniques. Before the biopsy, genetic tests are necessary: karyotype, CFTR (cystic fibrosis transmembrane conductance regulator) gene mutation, AZF (azoospermia factor) deletions because up to 20% of azoospermic men have genetic abnormalities. Types of testicular biopsy: 1. Open (surgical) classic TESE (testicular sperm extraction), microscopic m-TESE (microdissection-TESE); microsurgical MVAS (microsurgical vasal sperm aspiration); MESA (microsurgical epididymal sperm aspiration); 2. Percutaneous (minimal invasive techniques): PVAS (percutaneous vasal sperm aspiration), PESA (percutaneous epididymal sperm aspiration); TeFNA (testicular, fine needle aspiration) gives only cytological evaluation; TESA (testicular sperm aspiration) shows precise architecture of testicular tissue. Specimen evaluation by Johnsen score (Johnsen: Hormones, 1970, 1, 2–25) is done and include analysis of oncological aspects as well according to high risk of cancer (10–20 times) in azoospermic men (Olesen: Fertil Steril. 2017, 107, 74–82). Cryoprotection of testicular tissue should be done. M-TESE is recommended by European Association of Urology (EAU, 2017).

Birute Zilaitiene, Jonas Ceponis, Lina Lasaite

LATE ONSET MALE HYPOGONADISM: BENEFITS AND RISKS OF TESTOSTERONE REPLACEMENT THERAPY

Department of Endocrinology and Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; e-mail: birute.zilaitiene@lsmuni.lt

Male hypogonadism is a clinical syndrome caused by testosterone (T) deficiency which adversely affect multiple organ function and quality of life. Late onset male hypogonadism (LOH) is consequence of the aging process, related to hypothalamic pituitary function and Leydig cell function deterioration.

Diagnosis of T deficiency is based on clinical manifestation along with T levels below the laboratory range. T deficiency should be suspected in numerous of chronic conditions. The pilot study in Lithuania demonstrated that 63 percent of type 2 diabetes inpatients has morning T concentration bellow 12nmol/l and in 37 percent of cases this concentration is bellow 8nmol/l (*Zilaitiene at al.*: 2017, unpublished).

Regular monitoring of the effectiveness and safety of testosterone replacement therapy (TRT) is essential especially during the first year of treatment. The confirmed benefits of TRT are improvement of libido and erectile function, increase of hematocrit, positive effect on skeletal muscles, improvement in congestive heart failure (*Tyagi*: Rev Urol., 2017, 19, 1, 16–24). But there are evidences of the following risks: increased risk of polycythemia and thromboembolic cardiovascular events; marginal increase in prostate volume and prostate specific antigen (PSA) level; recurrence and rapid progression of high risk prostate cancer and potential exacerbation of subclinical residual residual prostate cancer; impairment of spermatogenesis. When TRT is initiated T concentration, hematocrit, PSA should be checked at baseline, at three, six months and then annually following onset of treatment, a digital rectal examination – at baseline, at six months and then annually (*Morales et al.*: CMAJ, 2015, 8, 187, 1369–1377).

It is still unclear if TRT has positive effect on mood and cognitive function. Our recently published study demonstrated beneficial effect in cognitive functioning, but not in emotional state and quality of life in hypogonadal men after two-year testosterone replacement therapy (*Lasaite at al.*: Andrologia, 2017, 49, 1–10). Also

data regarding cardiovascular risks and prostate health during TRT is still lacking.

So, TRT is safe and effective method to improve T deficiency symptoms in men, but should be avoided in cases of erythrocytosis, severe untreated obstructive sleep apnoe, severe congestive heart failure and in patients with suspected prostate or male breast malignancy.