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SUMMARIES OF THE 3RD
CONGRESS OF THE EASTERN
EUROPEAN SOCIETY
OF ENDOMETRIOSIS
AND INFERTILITY
AND THE 6TH NATIONAL
CONFERENCE OF ROMANIAN
SOCIETY OF HPV

• Poiana Brașov, Romania, July 1-3 2021 •

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MEDICHUB MEDIA SRL
Green Gate Office Building, 22 Tudor Vladimirescu Blvd.,
11th Floor, District 5, 050883, Bucharest, Romania
Phone: (031) 425.40.40, Fax: (031) 425.40.41
E-mail: redactia@medichub.ro
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AL III-LEA CONGRES NAȚIONAL AL SOCIETĂȚII DE ENDOMETRIOZĂ ȘI INFERTILITATE EST-EUROPEANĂ

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Kisspeptin and implications in polycystic ovary syndrome

Mona Akad, Răzvan Socolov

"Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

Introduction. Kisspeptin is a hypothalamic peptide that plays an essential role in the upstream of gonadotropin-releasing hormones by mediating sex steroid feedback and metabolic regulation of the reproductive axis. Recent studies have shown its role in puberty onset, in the maintenance of normal reproductive function and in metabolic and hormonal disturbances leading to polycystic ovarian syndrome (PCOS). Encoded by the *KISS1* gene, it was first isolated from human placental tissue, but later on, its presence has been discovered in other numerous organs. PCOS is a common disorder characterized by polycystic ovaries, chronic anovulation and hyperandrogenism. Considering the existing evidence of kisspeptin regulating the hypothalamo-pituitary-gonadal axis, it is only a matter of time until this neuropeptide will play an important role in the diagnosis and management in PCOS. **Materials and method.** During January 2021 and May 2021, in the "Elena Doamna" Clinical Hospital of Obstetrics and Gynecology, Iași, a prospective study, showing the implications of kisspeptin in patients diagnosed with PCOS, was initiated. Sixty female patients were included in our study. They were divided into two groups, the control group consisting in

30 healthy patients with no evidence of PCOS or other endocrinological disorders, and a test group consisting in patients with PCOS. All patients were rigorously selected by respecting inclusion and exclusion criteria, and all of them gave their consent in participating in this study. Eight hormonal parameters were taken into consideration: kisspeptin, luteinizing hormone, follicular stimulant hormone, testosterone, estradiol, prolactin, insulin, and glycemic index. All laboratory tests were performed during follicular period. All patients benefited from clinical examination and pelvic echography. **Results.** When observing the results in our PCOS group, we encountered higher levels of kisspeptin, up to 200 pg/ml, and LH/FSH modified reports. The control group showed overall lower levels of kisspeptin, with values beneath 100 pg/ml. **Discussion.** Recent studies have clearly shown the involvement of kisspeptin and its receptors in the reproductive axis and in PCOS complicated by infertility. Further studies are needed in order to identify new and better therapeutic schemes for patients suffering from PCOS infertility.

Keywords: kisspeptin, polycystic ovary syndrome, infertility

Implications of endometriosis on reproductive parameters in *in vitro* fertilization

Dragoș Albu^{1,2,3}, Alice Albu^{1,2,3}

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. ARTHOPE Bucharest, Romania

3. MedLife, Department of Maternal-Fetal and Reproductive Medicine, Bucharest, Romania

Introduction/objective. Endometriosis is common in infertile women. *In vitro* fertilization (IVF) is one of the therapeutic possibilities in infertility associated with endometriosis. Whether endometriosis has a suboptimal response to IVF is not clearly established. **Methodology.** We conducted a retrospective study in the MedLife Department of Maternal-Fetal and Reproductive Medicine. The medical data of patients with infertility of any causes who underwent IVF between January 2013 and August 2017 were reviewed. Only patients with all available data were included: age, causes of infertility, height, weight, dose of gonadotropins used for controlled ovarian stimulation, serum anti-Müllerian hormone (AMH) level, number of oocytes recovered, ovarian surgery data or anterior tubal. **Results.** A total number of 1708 patients were included in the study, 188 patients with endometriosis and 1520 patients without endometriosis. The patients had a mean age of 34.7 years old, an average serum AMH level of 2.92 ng/ml and an average BMI of 22.8 kg/m². The patients

with endometriosis were younger ($p=0.003$), had lower serum AMH ($p=0.007$) and a lower number of recovered oocytes (6.68 ± 4.73 versus 7.46 ± 4.87 ; $p < 0.05$) compared with patients without endometriosis. In a multivariate regression model with AMH as a dependent variable, the presence of endometriosis was negatively associated with serum AMH ($\beta = -0.093$; $p = 0.001$) after adjusting for age, BMI and cause of infertility. In the subgroups of patients, the negative relationship between endometriosis and serum AMH level after adjustment was maintained at those of 35 years old and over ($\beta = -0.107$; $p = 0.008$) and under 35 years old ($\beta = -0.082$; $p = 0.05$) and in patients with normal ovarian reserve ($AMH \geq 1.1$ ng/ml, $\beta = -0.071$; $p = 0.039$), but not in those with low ovarian reserve. **Conclusions.** Our study suggests that, although in endometriosis the AMH production appears to be low, serum AMH levels still overestimate the number of oocytes recovered after controlled ovarian stimulation for IVF.

Keywords: endometriosis, IVF, AMH

Preoperative diagnosis of endometriosis – transvaginal ultrasound versus magnetic resonance imaging

Alexandra Bausic^{1,2}, Andrei Manu¹, Cătălin Coroleucă^{1,2}, Ciprian Coroleucă^{1,2}, Diana Comandașu^{1,2}, Diana Mihai^{1,2}, Elvira Brătîlă^{1,2}

1. "Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Introduction. Endometriosis is a common gynecological condition among women of childbearing age, associated with chronic pelvic pain, dysmenorrhea, infertility and impaired quality of life. Although the internationally accepted gold standard is the diagnostic laparoscopy, the preoperative noninvasive diagnosis methods – clinical examination, transvaginal ultrasound and magnetic resonance imaging (MRI) – are an important step in the correct preoperative diagnosis of endometriosis. The aim of this paper is to determine the ideal method of preoperative noninvasive diagnosis depending on the symptoms and location of endometriosis lesions, whether clinical examination and transvaginal ultrasound are sufficient or when MRI examination is necessary. **Methodology.** We performed, on a group of 96 patients diagnosed with endometriosis, imaging examination by transvaginal ultrasound and MRI before the surgical treatment of the lesions, with the collection of biological samples for histopathological examination. The results obtained after the intervention were observed, comparing the lesions identified preoperatively with those excised during surgery. **Results.** MRI provides accurate information for the staging of deep endometriosis, especially when the case does not allow

a transvaginal ultrasound examination – it is limited by chronic pelvic pain, *virgo intacta* or obese patient. MRI is used when the clinical examination and ultrasound do not identify lesions in symptomatic patients (parametric lesions, uterosacral ligaments). The association of MRI increases the sensitivity of transvaginal ultrasound in the diagnosis of endometriosis in these cases (70.3% compared to 11.3%). Large endometriosis lesions that can be easily identified on clinical examination and ultrasound do not require MRI (rectal nodules $d \geq 2$ cm, endometriomas $d \geq 4$ cm). For intestinal endometriosis, MRI and ultrasound have similar efficiency (83.78% and 87.75%). **Discussion and conclusions.** Although it is not a routine investigation in all patients suspected of having endometriosis, MRI is effective in identifying the lesions. It is necessary for the gynecologist to request an MRI investigation when the transvaginal ultrasound is insufficient or cannot be performed. The methods depend on the experience of the gynecologist and radiologist in making a preoperative assessment of the lesions, so that the surgical treatment is performed in the most complete way possible.

Keywords: endometriosis, transvaginal ultrasound, MRI

Poor responders: what is new in 2021? Are we rising to the challenge?

Alina-Elena Bordea^{1,2}, Mihaela Braga¹, Ioana Iordache³, Cristiana Odukoya³, Andreea Carp-Velișcu^{1,2,3}, Elvira Brătîlă^{2,3}

1. Embryos Fertility Clinic, Bucharest, Romania

2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

3. "Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

Introduction. In the field of human assisted reproduction, patients with low ovarian reserve are one of the main challenges for the infertility specialists. This is due to the low number of oocytes obtained after controlled ovarian stimulation cycles. **Materials and method.** As many studies reveal, the number of oocytes is directly proportional to the rate of blastocysts and the rate of pregnancy. This paper is a review of the literature, with the role of highlighting the news in the field. **Results.** What can we do for these patients to maximize their

chances of pregnancy? Dualstim, luteal phase stimulation, ovarian PRP and growth hormone therapy are just some of the latest options that poor responders seem to benefit from. **Conclusions.** As we well know, there are no effective methods to increase the ovarian reserve, so the poor responders are always in the center of scientific research, out of a desire to improve the pregnancy rate and the live birth rate.

Keywords: progesterone priming, controlled ovarian stimulation, freeze all

Ovarian reserve after surgery of endometriosis cysts

Radu Chicea

Faculty of Medicine, "Lucian Blaga" University of Sibiu, Romania

Introduction/objective. Endometriosis is one of the main causes of infertility in patients at risk. Surgical treatment – most often laparoscopic – leads, with the removal of the cyst lining and monopolar or bipolar coagulation of the remaining tissue, to a significant reduction of the ovarian parenchyma, with a significant reduction of the ovarian reserve. The aim of the study is to evaluate, through a retrospective study, the ovarian reserve after surgery for endometriotic cysts with bipolar electrocoagulation of the cyst implantation bed. **Methodology.** We evaluated 15 cases of patients with unilateral or bilateral ovarian cyst laparoscopically operated, with the removal of the cyst capsule and hemostasis by superficial bipolar coagulation to reduce the

depth of coagulation as much as possible. The ovarian reserve was evaluated in order to assess the severity of the decrease by monitoring two parameters: AMH and FSH values before and after surgery. **Results.** Ovarian cyst surgery is constantly followed by an increase in FSH levels and a decrease in AMH levels, more pronounced in bilateral ovarian cyst surgery. **Discussion and conclusions.** Electrocoagulation after the laparoscopic excision of ovarian cysts is associated with a significant reduction in ovarian reserve, which is partly a consequence of reduced ovarian parenchyma and the number of ovarian follicles and partly to the damage of the vascular system.

Keywords: ovarian cyst, laparoscopic ovarian cystectomy, electrocoagulation, ovarian reserve

Dynamics of the influence of the coronavirus pandemic on the addressability of infertility patients

Roxana Covali¹, Demetra Socolov², Ioana Păvăleanu¹, Diana Popovici¹, Mona Akad¹, R. Socolov¹

1. "Elena Doamna" Clinical Hospital of Obstetrics and Gynecology, Iași, Romania

2. "Cuza Vodă" Clinical Hospital of Obstetrics and Gynecology, Iași, Romania

Objective. The purpose of this paper is to highlight the extent of changes caused by the COVID-19 pandemic on the addressability and pathology of infertility patients. **Methodology.** In a retrospective study, we evaluated all consecutive patients who were referred to our hospital for hysterosalpingography between April 1, 2020 and March 31, 2021 (study group, n=12), compared to patients from the previous period, April 1, 2019 – March 31, 2020 (control group, n=116). **Results.** Variations between the two groups were highlighted, in terms of age, urban background, living in other counties, referring doctor outside the hospital (31.83 years old; 50%; 16.66%; 0% in the study group versus 32.5 years old; 68.1%; 26.72%; 26.72%

in the control group). Significant variations were observed in terms of uterine pathology: bicornuate uterus and endometriosis (8.33% in the study group versus 2.58% in the control group). The proportion of right hydrosalpinx (25% versus 7.78%) and left hydrosalpinx (16.66% versus 10.34%) also increased significantly. **Conclusions.** The coronavirus pandemic reduced the addressability of patients with infertility to 10.3% compared to the previous year, and significantly increased the proportion of patients discovered with bicornuate uterus, endometriosis and hydrosalpinx.

Keywords: hysterosalpingography, coronavirus, infertility

Endometriosis-associated ovarian cancer

Mihai Cristian Dumitrașcu^{1,2}, Cătălin-George Nenciu³, Adina-Elena Nenciu²

1. Departments of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, Bucharest University Emergency Hospital, Romania

3. Department of Obstetrics and Gynecology, "Sf. Ioan" Clinical Emergency Hospital, "Bucur" Maternity, Bucharest, Romania

Ovarian cancer is the gynecological tumor with the highest mortality, with a prevalence of 3.7% of malignant pathology in women. Over 90% of ovarian tumors have an epithelial origin, the rest coming from germ or thecal cells. In recent years, ovarian cancer has been divided into two subtypes – type I and type II, the first type including low-grade cancers and borderline serous tumors, endometrioid tumors, mucinous tumors, and clear cell carcinoma. The relationship between endometriosis and ovarian cancer was first discussed by Sampson in 1927, based on the coexistence of ovarian carcinoma with endometriosis in the same ovary,

similar histological pattern, and the absence of other malignancies with another location. In 1953, Scott highlighted the histopathological transition from benign endometriosis to cancer. Currently, the prevalence of ovarian cancer in people with endometriosis varies between 0.7% and 17%. Molecular medicine and genetics have allowed the understanding of the pathogenetic processes of endometriosis as a precursor to cancer. Currently, the malignant potential of endometriosis is recognized, thus leading to the need for proper long-term patient management.

Keywords: ovarian cancer, endometriosis

Why do we fail the early diagnosis of endometriosis and adenomyosis?

Corina Grigoriu^{1,2}, Lucica Eddan Vișan², Andreea Elena Constantin², Gina Ionescu-Anculete², Andra Bălan², Irina Horhoianu^{1,2}

1. Departments of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, Bucharest University Emergency Hospital, Romania

Introduction. Patients diagnosed in advanced stages of endometriosis and/or adenomyosis are still common in medical practice, although the advances in imaging are considerable. This delayed diagnosis is determined by a low degree of clinical suspicion. **Materials and method.** For this reason, we consider appropriate to review the diagnostic criteria, starting from the anamnesis data (personal and heredocolateral history, menstrual history, gynecological and obstetrical history) and the clinical and imaging examination. **Results.** In patients with endometriosis, the main symptom is pelvic pain, in its various forms (dysmenorrhea or dyspareunia). The characteristics of pelvic pain (diffuse or crampoid) must be correctly differentiated from that of pelvic inflammatory disease, with which it may coexist. From the anamnesis, we can insist on the characteristics of dysmenorrhea, which can occur frequently one to two days before menstruation, persists and lasts after its end. Urinary or digestive symptoms accentuated during menstruation are also suggestive (dysuria, diarrhea, dyschezia). The detailed clinical examination and the imaging investigations reveal the diagnosis. In

the case of adenomyosis, the anamnesis reveals dysmenorrhea, most often primary, to which is added the progressive increase of the amount of menstrual blood lost (up to menorrhagia). The patient may also report chronic pelvic pain, and in 10% of cases there is dyspareunia. The patient may have a history of diagnoses and treatments for endometriosis, endometrial polyps or even endometrial hyperplasia, with which there are associated. One of the most common associations is with the fibromatous uterus/uterine fibroids. There may be a history of infertility or failure of assisted human reproduction procedures. **Conclusions.** The early diagnosis in endometriosis allows the early adoption of a conservative medical attitude, with a beneficial impact not only on pain control, but especially on the patient's fertile prognosis. The early diagnosis in adenomyosis allows a better control of uterine hemorrhagic pathology, with the timing of a potential surgery and a better quality of life of the patient (for example, by avoiding anemia).

Keywords: endometriosis, adenomyosis, early diagnosis

Preneoplastic alterations in abdominal wall endometriosis

Anca-Maria Istrate-Ofițeru^{1,2,3}, D. Ruican¹, L.M. Dîră¹, Elena-Iuliana-Anamaria Berbecaru¹, Cătălina Rănescu¹, Ana-Maria Petrescu¹, Maria Cristina Comănescu¹, Ileana Drocaș¹, G.L. Zorilă¹, D.G. Iliescu¹

1. Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania

2. Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania

3. Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

Introduction. Abdominal wall endometriosis is a frequent pathology, more and more common due to the increase in the percentage of births through caesarean section. The endometrial tissue can suffer certain structural and functional changes which can be detected by the immunohistochemical examination. These changes may lead to normal cell transformation in some patients with preneoplastic alterations (hyperplasia, dysplasia) and then evolving to neoplasia. **Objective.** The evaluation of how the inflammatory system is involved in cellular alteration and the observation of the preneoplastic (hyperplastic) transformation of areas of interest. **Experimental part.** This is a retrospective study of 20 patients admitted in the Obstetrics-Gynecology II Clinic, Emergency County Hospital of Craiova, between 2016 and 2021, which presented a history of caesarean section. The diagnosis of abdominal wall endometriosis was presumed due to the accentuated symptoms and the presence of a mass at the caesarean section scar level detected by ultrasound investigation. The patients were then biopsied and the excision of the endometriotic nodules was performed. The histopathological examination

established the final diagnosis. **Results and discussion.** The patients included in the study were between 17 and 56 years old. We noticed that preneoplastic cellular changes (endometrial hyperplasia) occur more frequent in older aged patients. Cytokeratin 7 (CK7) is found in both normal and neoplastic endometrial cells and can be used as a differential diagnosis marker, as it is negative in ovarian or digestive carcinomas. Anti-B-cell lymphoma-2 (Bcl-2)/phosphatase and tensin homolog (PTEN) antibody reveal immunolabeled ectopic endometrial cells, which may have suffered preneoplastic alterations. Anti-tryptase/Cluster of Differentiation 68 antibody demonstrates the presence of many mast cells/macrophages involved in the immune reaction around the endometriosis foci. **Conclusions.** A multitude of inflammatory, hormonal and mechanical factors are involved in the development of endometriosis. The presence of cellular apoptosis inhibiting genes increases the cell division rate, and the strong immune response can influence the malignant transformation of endometriosis.

Keywords: endometriosis, preneoplastic alterations, immunohistochemistry

Endometriosis and subfertility: a systematic review

Dimitrios Kanellopoulos^{1,3}, Dimitra Karagianni², Grigorios Patsouras³, Konstantinos Patsouras³, Nikolaos Nikiteas⁴,
Andreas C. Lazaris², Dimitrios Iliopoulos¹

1. Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, National and Kapodistrian University of Athens, Greece

2. Department of Pathology, National and Kapodistrian University of Athens, Greece

3. Department of Obstetrics and Gynecology, Tzaneio Hospital, Athens, Greece

4. Propaedeutic Department of Surgery, National and Kapodistrian University of Athens, Greece

Introduction. Endometriosis causes adhesions and lesions of the uterine tissues, resulting in the fallopian tubes not functioning properly. It creates cysts in the ovaries, which are the very cause of ovarian damage. It is not only the cysts that wear out the ovaries but also the surgeries that are performed to remove them. In fact, the more surgeries there are, the more damage is caused to the ovaries (Wei et al., 2020). Endometriosis depends on estradiol (E2) for its development, a hormone to which the success of pregnancy is due. In addition, endometriosis stops progesterone (P4) signaling (Houshdaran et al., 2020). This is due to chronic inflammation, lesions and deformities of tissues, but also to epigenetic changes in chromatin that determine cellular responses to mitogens and differentiation signals (Houshdaran et al., 2020). **Materials and method.** A recent literature search was conducted on the basis of PubMed with the keywords: “endometriosis”, “fertility”, “endometriosis and infertility”, “inflammatory reaction in endometriosis” and “endometriosis and epigenetics”. Based on the articles of Houshdaran et al., 2020, Wei et al., 2020, Qi et al., 2020 and Rasheed and Hamid, 2020, we try to find the answers to questions about the endometriosis and its effect on

fertility. **Results.** The development of endometriosis is dependent on estrogen, to which the endometrial tissues are hypersensitive. Although estrogen is required to initiate and promote the reproductive cycle, however hypersensitivity in women with endometriosis adversely affects reproductive function (Rasheed and Hamid, 2020). Endometrial lesions are present in an inflammatory microenvironment with higher local concentrations of cytokines, such as tumor necrosis factor α (TNF- α) (Kocbek et al., 2016; Qi et al., 2020). TNF- α increases the expression of phosphorylated IKKB, an important protein present in multiple signaling pathways that affects gene transcription, proliferation and apoptosis (Kocbek et al., 2016; Qi et al., 2020). Inflammation in the endometrial environment affects the quality of oocytes indirectly by cytokines in the peritoneal fluid, modifying ovulation and oocyte spindles, thus affecting both oocyte maturation and fertilization (Singh et al., 2016; Rasheed and Hamid, 2020). **Conclusions.** Inflammation and its derivatives negatively affect the quality of oocytes and make the environment of the uterus inhospitable to the implantation of the fetus.

Keywords: endometriosis, subfertility, inflammation

Pathogenesis and pathophysiology of endometriosis: a systematic review

Dimitrios Kanellopoulos^{1,3}, Dimitra Karagianni², Grigorios Patsouras³, Konstantinos Patsouras³, Nikolaos Nikiteas⁴, Andreas C. Lazaris², Dimitrios Iliopoulos¹

1. Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, National and Kapodistrian University of Athens, Greece

2. Department of Pathology, National and Kapodistrian University of Athens, Greece

3. Department of Obstetrics and Gynecology, Tzaneio Hospital, Athens, Greece

4. Propaedeutic Department of Surgery, National and Kapodistrian University of Athens, Greece

Introduction. Endometriosis has been shown to be caused by abnormalities in molecular cataracts involving estrogen, progesterone and several prostaglandins (Günel et al., 2019). Three theories have been proposed to establish endometriosis (Chantalat et al., 2020). Retrograde menstruation is the most prevalent. Other studies show that we need to study endometriosis following in the footsteps of cancer and metastatic transcription factors (Eychenne et al., 2019; Chantalat et al., 2020). This review describes a summary of the molecular, metabolic and immune changes that occur during endometriosis, these changes contributing to its promotion and establishment. **Materials and method.** Articles were searched in PubMed, and articles from the last five years were selected. The pathogenesis of endometriosis remains unclear, however three theories have been proposed for the cause of endometriosis. **Results.** Retrograde menstruation, in which the epithelial and stromal cells of the uterus migrate and implant in the peritoneal cavity through the fallopian tubes, is the most accepted mechanism for the pathogenesis of endometriosis (Chantalat et al., 2020). However, retrograde menstruation does not explain the occurrence of endometriosis in extrapelvic areas. A second theory about the mechanism of initiation of endometriosis suggests that the epithelial peritoneal lining can be transformed into endometrial tissue under the influence of stimuli: this is the theory of colonic metaplasia (Chantalat et al., 2020). Another theory, for benign lymphatic or hematogenous metastases, proposes the extraperitoneal proliferation of endometrial tissue through the lymphatics and suggests that ectopic endometrial cells have migratory capabilities (Eychenne et al., 2019; Chantalat

et al., 2020). The transcription factor Specificity protein 1 (Sp1) promotes ectopic endometrial proliferation and is directly regulated by miR-25-3p (Shen et al., 2020). It is noted that the Sp-1 gene has been found to interact with many regulatory miRNAs that promote carcinogenesis and the development of various cancers. Hence, we need to focus on the study of genes that cause cancer metastasis or to hub genes such as Sp-1 that activate carcinogenic pathways. Glutamine/glutamate metabolism has been found increased in many types of cancer, such as in endometriosis, and several studies have correlated glutamine concentration with cell migration (Berkes et al., 2013; Zhang et al., 2017; Murgia et al., 2021). An increase in glutamine in specific areas of the brain in women with chronic pelvic pain associated with endometriosis suggests a role in the onset or worsening of pain in patients (As-Sanie et al., 2015; Murgia et al., 2021). Finally, estrogen and estrogen receptors play the most dominant role. During endometriosis, estrogen levels are dramatically increased. The dominance of estrogen does not necessarily mean that a woman has extremely high levels of estrogen, but that the ratio of estrogen to progesterone is very high, and there is no balance (Chantalat et al., 2020). **Conclusions.** Endometriosis is accompanied by changes in gene expression and many of them involve transcription factors that cause carcinogenesis and invasion of cells such as Sp-1. Also, it is accompanied by changes in metabolic pathways. Increased glutamate metabolism is observed, which contributes to the severity of symptoms and pain.

Keywords: endometriosis, pathophysiology, hormones, estrogen receptors, glutamine

Research on the effect of endometriosis on fertility in an animal model

Dimitrios Kanellopoulos^{1,3}, Dimitra Karagianni², Vasilios Pergialiotis¹, Grigorios Patsouras³, Konstantinos Patsouras³, Nikolaos Nikiteas⁴, Andreas C. Lazaris², Dimitrios Iliopoulos¹

1. Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, National and Kapodistrian University of Athens, Greece

2. Department of Pathology, National and Kapodistrian University of Athens, Greece

3. Department of Obstetrics and Gynecology, Tzaneio Hospital, Athens, Greece

4. Propaedeutic Department of Surgery, National and Kapodistrian University of Athens, Greece

Introduction. Endometriosis is a condition of female reproductive age where endometrial tissue (glands and layer) grows outside the uterus. Endometriosis is characterized by many researchers as an enigmatic disease and remains, even today, a serious condition that affects the quality of a woman's life and her reproductive capacity. Endometriosis can be surgically induced in rats, which exhibit similar symptoms to humans.

Materials and method. In our research, which was carried out at the Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, 24 female rats of Sprague Dowley® type, aged 3 months old and weighing 170-200 grams, were used for the development of an animal model for the study of endometriosis. Living and handling conditions were in line with Presidential

Decree 160/91, which governs the protection of animals used for research purposes. All rats were deprived of food 12 hours before surgery. On the day of surgery, they were randomly divided into four groups, consisting of six rats each. Group A consisted of healthy female rats (control group). Group B consisted of rats with ovarian endometriomas. Group C consisted of rats with disseminated intraperitoneal endometriosis, while Group D consisted of rats with extraperitoneal endometriosis. In groups B, C and D, the disease was experimentally induced by transplanting fragments of endometrial tissue into ectopic sites. **Conclusions.** In our experimental model, we observed that endometriosis affects fertility by reducing the number of follicles.

Keywords: endometriosis, subfertility, rats

Surgical induction of endometriosis in rats. A systematic review

Dimitrios Kanellopoulos^{1,3}, Dimitra Karagianni², Vasilios Pergialiotis¹, Grigorios Patsouras³, Konstantinos Patsouras³, Nikolaos Nikiteas⁴, Andreas C. Lazaris², Dimitrios Iliopoulos¹

1. Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, National and Kapodistrian University of Athens, Greece

2. Department of Pathology, National and Kapodistrian University of Athens, Greece

3. Department of Obstetrics and Gynecology, Tzaneio Hospital, Athens, Greece

4. Propaedeutic Department of Surgery, National and Kapodistrian University of Athens, Greece

Introduction. Endometriosis can be surgically induced in rats, which exhibit similar symptoms to humans (Günel et al., 2019). **Materials and method.** The data were taken from PubMed and included studies from the recent years. In the studies we selected, the researchers induced endometriosis by transferring endometrial tissue from the uterus to extrauterine areas. **Results.** In their study (Cuevas et al., 2018), the researchers induced endometriosis in female rats. In endometriosis areas, still degenerated mast cells were observed. Mast cell secreted proteases play an important role in fibrinogenesis and endometrial tissue migration (Cuevas et al., 2018). Free radical scavengers, such as melatonin and erythropoietin, have been found to reduce endometrial lesions by their antioxidant properties (Yildirim G, et al., 2010; Günel et al., 2019).

In their study (Günel et al., 2019), the authors caused endometriosis in rats and after induction they administered estrogen to cause greater damage. In the group of rats administered by erythropoietin, endometrial foci and histopathological scores were both found to be reduced. After 20 days of erythropoietin treatment in rats, the lesions were further reduced (Chadha et al., 2008). **Conclusions.** Rats have been widely used in endometriosis models, as they show similar symptoms to humans. The accumulation of estrogen, the innervation of the hypothalamus and the oxygenation of the area through the development and differentiation of erythrocytes play an important role in the manifestation of symptoms.

Keywords: rats, endometriosis, estrogen, stress, erythropoietin

Alternatives in endometriosis: myth or reality?

Cristina Elena Mandici¹, Roxana-Daniela Mătășariu¹, Mihaela Grigore^{1,2}

1. Department of Mother and Child Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

2. "Cuza Vodă" Clinical Hospital of Obstetrics and Gynecology, Iași, Romania

Introduction. Endometriosis is considered an enigmatic malady with chronic symptomatology, having a negative impact on patients' quality of life. Surgical interventions and hormonal substitution therapy represent the current treatment for endometriosis. Adopting a long-term strategy may require a combination of surgical treatments, medical treatments and alternative therapies, in order to suppress the painful symptomatology and to control the other symptoms associated with endometriosis. **Methodology.** The research and the analysis of articles published in the specialized literature to assess the main options for the alternative treatment in endometriosis and the suppression rate of symptomatology. **Results.** The efficiency of conventional endometriosis treatment is currently limited. Consequently, it is necessary to exploit complementary and alternative strategies of therapy, to minimize the adverse effects of ongoing treatments. Several studies have shown that people suffering from endometriosis who have adopted a gluten-free diet have presented an improvement in ameliorating the painful symptoms and, at the same time, it has been concluded that an

increased intake of antioxidants has decreased the oxidative stress, responsible for the inflammation. Various medicinal plants have been investigated for their pharmacological properties in endometriosis therapy, their effects being linked to different compounds such as flavonoids and phenolic acid, reporting antiinflammatory, proapoptotic, antioxidant and immunomodulatory functions. Furthermore, some substances have been linked to a powerful effect ascribed to phytoestrogens which modulate estrogen-related activity. **Discussion and conclusions.** Women suffering from endometriosis are interested in using complementary and alternative medicine. The majority of female patients have used at least one CAM method to relieve the symptoms associated with the disease. Although promising, the available evidence is based on a limited number of well-conducted clinical studies. Therefore, properly conducted clinical studies are mandatory to get conclusive results regarding the promising role of complementary and alternative methods in endometriosis.

Keywords: endometriosis, complementary and alternative medicine, phenolic compounds, oxidative stress

Parietal endometriosis

Andrei Manu¹, Alexandra Baușic¹, Bogdan Cătălin Coroleucă¹, Andrei Ciprian Coroleucă^{1,2}, Diana Comandașu^{1,2}, Elvira Brătilă^{1,2}

1. "Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Introduction. Endometriosis of the abdominal wall is a condition defined by the presence of endometrial tissue in the subcutaneous adipose tissue and in the muscles of the abdominal wall. The diagnosis can be difficult due to the fact that the symptoms are not specific. The patients present with catamenial abdominal pain and palpable abdominal tumor. Endometriosis of the abdominal wall usually affects women of fertile age and most commonly occurs on the post-caesarean scar. The diagnosis can be made by ultrasound or magnetic resonance imaging, correlated with medical history and clinical examination. The treatment of choice is surgical resection of the endometrioma. **Methodology.** During 2019 and 2020, 146 patients diagnosed with endometriosis were treated in our clinic. Eleven of these cases were diagnosed and treated for abdominal wall endometrioma. **Results.** 16.06% of the patients diagnosed with endometriosis were diagnosed with abdominal wall endometrioma. Of the 11 cases of parietal endometriomas, 45% also associated deep endometriosis lesions of the pelvic peritoneum,

unilateral or bilateral endometriotic cysts, deep endometriosis nodules in the parameters or uterosacral ligament or intestinal nodules. The average age of patients was 35 years old. The results of the histopathological examination confirmed in all cases the diagnosis of parietal endometriosis. In two of the 11 patients with abdominal wall endometrioma, polypropylene mesh was used to close the aponeurotic defect. **Conclusions.** Endometriosis of the abdominal wall is usually manifested by palpable tumor formation accompanied by cyclic abdominal pain. Ultrasound together with a correct clinical examination and the patient's history can guide the diagnosis. MRI is nonspecific but it can help diagnose node extension and the deep pelvic endometriosis lesions. In our experience, abdominal wall endometriomas occur quite frequently, with or without deep endometriosis. The number of cases diagnosed with parietal endometriosis is increasing, in line with the increase in the number of caesarean sections.

Keywords: deep endometriosis, abdominal wall endometrioma, surgical resection, cyclic abdominal pain

Use of autologous hematopoietic bone marrow stem cells to improve fertility

Diana Mihai¹, Prabhu Chandra Mishra², Cristina Diana Pomană¹, Elvira Brătîlă³

1. "Carol Davila" University of Medicine and Pharmacy Doctoral School, Bucharest, Romania

2. StemMax Research & Therapeutics Pvt., New Delhi, India

3. "Carol Davila" University of Medicine and Pharmacy; "Prof. Dr. Panait Sirbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

Objective. Hematopoietic autologous stem cells are undifferentiated cells with the potential to multiply and differentiate into different types of mature cells, which are obtained by harvesting bone marrow from the iliac crest, for example, from the same patient, in the same intervention as the treatment. The goal is to rejuvenate the ovaries in patients with premature ovarian failure and endometrial regeneration in pathologies such as Asherman syndrome. This treatment can give women the chance to have a pregnancy without donated oocytes, improves the quality of life of women suffering from premature menopause and restores fertility. **Materials and method.** We performed an analysis of studies in the literature on the results of treatment with hematopoietic autologous stem cells in improving fertility. **Results.** Studies that have evaluated patients who want a pregnancy but have been advised to use donated oocytes (due to a poor ovarian response to controlled ovarian hyperstimulation for *in vitro* fertilization or due to low ovarian reserve and low oocyte quality) show promising results.

Laparoscopic injection of stem cells proved superior to transvaginal injection. The use of autologous bone marrow stem cells has proven superior to the use of adipose tissue stem cells and is a minimally invasive technique with low associated risks. After the procedure, studies show follicular growth, improved vascularity, increased follicular and stromal cell proliferation and also reduced apoptosis and cell atresia. In refractory cases of Asherman's syndrome or endometrial atrophy for various reasons, studies reveal that the instillation of hematopoietic autologous stem cells has had favorable results in endometrial regeneration and the reappearance of menstruation and fertility. Studies also include obtaining spontaneous pregnancies after stem cell treatment in patients with a history of IVF failure. **Conclusions.** Stem cell therapy may provide solutions for dozens of women suffering from ovarian failure, poor oocyte quality, premature menopause, infertility or endometrial pathology such as Asherman syndrome.

Keywords: hematopoietic autologous stem cells, premature ovarian failure, AMH

Bowel endometriosis – Bucharest endometriosis centre experience

Gabriel Mitroi

Provita Hospital, Bucharest, Romania

Introduction. Endometriosis is a chronic, inflammatory, estrogen-dependent condition which affects approximately 10-15% of reproductive-aged women. It is classified as genital versus extragenital. Affecting up to 37% of women with endometriosis, bowel endometriosis is the most common site for extragenital endometriosis and may present as deep dyspareunia, dyschezia, diarrhea or constipation, bloating, blood in the stool, pain with sitting, and chronic pain. It can line the bowel serosa or the subserosal area, or it can deeply infiltrate the muscularis or the mucosa. We present our three-year experience conducted in the Bucharest Endometriosis Centre, which proudly gathers multiple laparoscopic specialists who provide patient-targeted multidisciplinary treatment of bowel endometriosis. **Methodology.** Our team consists of three gynecologists, two general surgeons, one urologist, one consultant radiologist and five ART (assisted reproduction techniques) specialists. In three years, we managed 557 endometriosis cases in women with ages between 21 and 52 years old. All surgeries were done laparoscopically. **Results.** Among all

our cases, 414 patients proved to have deep infiltrating endometriosis and 226 patients had bowel endometriosis. We emphasize the chosen types of excision, their location and association pattern of the lesions, along with the intraoperative incidents and complications. **Discussion and conclusions.** The benefits of excisional surgery are undeniable, including not only pain relief, but improvement of the quality of life, potential increase of fertility and cancer prophylaxis. The surgical approach of the bowel endometriosis splits into three categories: shaving, disc resection, and segmental resection. It is influenced by the location of the bowel lesion, the depth of infiltration, the presence/absence of stricture and the number of lesions. Based on our extensive experience in conjunction with constant reviewing of the literature, we strongly advise that bowel endometriosis should be managed only by a multidisciplinary endometriosis-specialized team, which is able to diagnose and treat it accordingly, in a minimally invasive fashion.

Keywords: bowel endometriosis, laparoscopic surgery, multidisciplinary team

Ureteral and diaphragmatic deep infiltrating endometriosis – surgical management in two challenging cases

Gabriel Mitroi

Provită Hospital, Bucharest, Romania

Introduction. Deep infiltrating endometriosis (DIE) represents infiltrative lesions with a depth more than 5 mm beneath the peritoneum surface. Besides the typical involvement, DIE can also impact the ureters and the diaphragm. We have encountered ureteral and diaphragmatic DIE more often than expected. We present two videos to demonstrate how we surgically managed this endometriosis phenotypes. **Methodology.** In our three-year experience, from a total of 557 managed cases of endometriosis, we encountered 57 cases of ureteral endometriosis and 47 cases of diaphragm endometriosis. **Results.** The first case is about a woman who was diagnosed in a urology department, with grade 3-4 uretero-hydronephrosis. After the placement of ureteral catheter (double J), she was hospitalized in our center for surgical treatment. The complete removal of the stenotic lesion was performed, with preserved integrity, against all the odds in favor for ureteral re-implantation. The second video displays the case of a patient who was operated one year before for bowel endometriosis with colorectal resection and diaphrag-

matic minor endometriosis lesions which were excised. Subsequently, the patient underwent ovarian stimulation within an ART (assisted reproduction technique) protocol. After this treatment, the patient accused severe pain localized in the chest, interscapular and in the right shoulder. Magnetic resonance imaging revealed infiltrative endometriosis lesion in the right hemidiaphragm that required excision and suturing of the diaphragm. **Discussion and conclusions.** Ureteral DIE incidence is cited as 0.1-1% and usually involves the lower one-third of its segment. Diaphragmatic endometriosis is a rare disorder. In 95% of cases, the lesions occur on the right hemidiaphragm. In contrast with ureteral endometriosis, which is mostly indolent but dangerous, the symptoms in diaphragmatic endometriosis may vary from intense chest pain to thoracic endometriosis syndrome (TES). Decompressive surgery is mandatory in ureteral endometriosis, as well as the full excision of diaphragmatic lesions.

Keywords: ureteral endometriosis, diaphragmatic endometriosis, DIE

Endometriosis – a benign pathology with malignant potential

Ioana Păvăleanu^{1,3,4}, R.V. Socolov^{1,3}, Raluca Bălan^{2,3}, Simona Eliza Giușcă², Ludmila Lozneau², Roxana Avădanei², Irina Draga Căruntu², Maricica Păvăleanu³, Cornelia Amălinei²

1. Mother and Child Health Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

2. Morphofunctional Sciences Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

3. "Elena Doamna" Maternity, Iași, Romania

4. Regional Institute of Oncology, Iași, Romania

Introduction/objectives. The capacity of endometriosis for malignant transformation is well known: either endometriosis implants can directly undergo malignant transformation, or both processes share a common precursor mechanisms and predisposing factors. Endometriosis-associated ovarian cancer (EOC) occurs in 60-80% of cases in association with atypical endometriosis and is represented by clear cell carcinoma (CCC) and endometrioid carcinoma (EC). The study seeks to identify atypical changes developed in endometriosis lesions as precursor lesions of ovarian carcinomas, as well as their association. **Methodology.** A retrospective analysis of 31 cases of endometriosis and 19 cases of CCC or EC was performed. Immunohistochemical markers were used to assess the existence of stem-like cells (BMI-1), and also the alteration of intercellular adhesion mechanisms (E-cadherin, beta-catenin) and of apoptosis and cell proliferation (CK18, Bax, Bcl-2, p53, Ki-67). **Results.** The progressive loss of BMI-1 expression with stage advancement demonstrates that BMI-1 can be considered as a prognostic factor in EOC. The

staining index of E-cadherin is intense in endometriosis and gradually decreases with the gradual evolution of cases diagnosed with malignancy. CK18 showed a high staining index in endometriosis, and in the malignant group a progressive reduction of the staining index was correlated with the stage progression. P53 expression in endometriosis was significantly lower compared to the expression in tumor tissue, indicating less aggressive behavior of endometriosis compared with malignant lesions. The Ki-67 index in tumor cells was reduced in more than half of the cases and was lower or even absent in endometriosis, as an indicator of less proliferative activity in the pathogenesis of endometriosis compared to malignant tumors. **Discussion and conclusions.** Endometriosis can be considered a precursor lesion of EOC, demonstrated both by their coexistence and the identification of intermediate lesions, and by the progression of various markers (of TEM, apoptosis and cell proliferation, respectively).

Keywords: ovarian cancer, clear cell carcinoma, endometrioid carcinoma, endometriosis

The fate of frozen embryos: their destruction, adoption or donation?

Cristina-Diana Pomană^{1,2}, Prabhu Chandra Mishra³, Elvira Brătîlă^{1,4}, Diana Mihai^{1,4}

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, "Sf. Ioan" Clinical Emergency Hospital, "Bucur" Maternity, Bucharest, Romania

3. StemMax Research & Therapeutics Pvt. New Delhi, India

4. "Prof. Dr. Panait Sirbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

Objectives. *In vitro* fertilization (IVF) includes a complex set of procedures used to improve fertility, prevent genetic problems, and help conceive a child. In most cases, this procedure results in more than one embryo. The couples have a major problem after IVF regarding the remained cryopreserved embryos and what should happen with it. **Materials and method.** We performed a research on the international studies about the fate of frozen embryos after obtaining the number of pregnancies desired by the patient. **Results.** There are some principles of bioethics that are very important for both patients and medicine: respect for autonomy, non-maleficence, beneficence and justice. There are specific laws that must

be respected, laws stipulated by the Societies of Human Reproduction and Embryology, the Declaration of Human Rights and various civil and criminal codes available, which differ in each country and state worldwide, and also the beliefs of the Christian religion. The couples can opt for donation or adoption meaning they can transfer the embryos to another couple. Another option is the destruction of the surplus embryos. **Conclusions.** This article provides a complete picture of patients, as well as doctors in general, in terms of justice, religion and bioethics on surplus frozen embryos remaining after obtaining the desired number of children.

Keywords: embryos, fertility, conception, bioethics

Therapeutic aspects of symptomatic adenomyosis

Cătălina Rănescu¹, Anca-Maria Istrate-Ofițeru^{1,2,3}, Elena-Iuliana-Anamaria Berbecaru¹, Andreea Vochin¹, D. Ruican¹, Iuliana Alina Dica¹, Rodica Daniela Nagy¹, Roxana Cristina Drăgușin¹, D.G. Iliescu¹, G.L. Zorilă¹

1. Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania

2. Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania

3. Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

Introduction. Adenomyosis is a benign uterine disease. It is represented by the presence of endometrial glands in the structure of the myometrium. It has become a common pathology. The symptoms are intense and usually affect the patient's daily life. Adenomyosis can be suspected based on the clinical and ultrasound aspects, and diagnosed by histopathological exam. It has multiple morphofunctional aspects, and sometimes it has important consequences on the patient's life. **Methodology.** This is a retrospective study, conducted between 2018 and 2021 in the Obstetrics-Gynecology Clinic II of the Craiova County Emergency Clinical Hospital, on a group of 40 patients, aged between 21 and 58 years old. The patients presented menometrorrhagia and pelvic-abdominal pain. The usual blood tests frequently revealed a certain degree of anemia, and the ultrasound examination showed suggestive aspects of adenomyosis. For some patients, a symptomatic treatment was necessary and in other patients, the surgical treatment. The samples were sent to the pathological anatomy department for the histopatho-

logical examination. The diagnosis of adenomyosis was confirmed by histopathological examination. In the classic hematoxylin-eosin staining, we observed areas with fibrocollagen tissue in full myometrium, groups of dilated cystic glands and endometrial stroma, with acute periglandular inflammation. The differential diagnosis with a possible metastasis with a digestive starting point was made using the immunohistochemical study with anti-estrogen receptor (ER) antibodies – positive reaction, anti-progesterone receptors (PR) – positive reaction, anti-cytokeratin 7 (CK7) – positive reaction, and anti-cytokeratin 20 (CK20) – negative reaction. **Conclusions.** The histopathological examination confirmed the existence of endometrial glands, positive for hormonal markers, and cytokeratins that are specific for the endometrial epithelium. The ultrasound examination proved to be a useful tool in the diagnosis of adenomyosis. It also helped us to guide the treatment and follow up the results.

Keywords: adenomyosis, pelviabdominal pain, ultrasound

Endometrial polyps and infertility – the experience of our clinic

Romina-Marina Sima^{1,2}, Anca Daniela Stănescu^{1,2}, Liana Pleș^{1,2}

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, "Sf. Ioan" Clinical Emergency Hospital, "Bucur" Maternity, Bucharest, Romania

Introduction. Endometrial polyps are often discovered in subfertile women. How polyps contribute to subfertility and pregnancy loss is uncertain, and the possible mechanisms are poorly understood. **Materials and method.** A prospective cohort type 1 study based on STROBE statement was designed. The study group included women diagnosed with endometrial polyps and infertility in the "Bucur" Maternity, "Sf. Ioan" Clinical Emergency Hospital, Bucharest, Romania, between January 2016 and December 2019. The diagnosis was established by ultrasound and hysteroscopy and confirmed during hysteroscopic procedure. **Results.** We performed 278 hysteroscopies during the study period. The study included 56 (20.14%) patients, aged between 28 and 46 years old (mean age: 29.57 years

old; standard deviation: 9.79) who associated infertility and endometrial polyps. The hysteroscopy confirmed the diagnosis of polyps made by ultrasound in 99.5% of cases. The main characteristics of the study group were as follows: urban area citizens (82%), non-smokers (73.2%) and obese women (65%). These women were diagnosed with primary (67.3%) and secondary infertility (32.7%). They had associated gynecological pathologies: uterine myomas in 1.7% of cases and adenomyosis in 2.3% of cases ($p < 0.001$). **Conclusions.** Patients diagnosed with endometrial polyps may associate infertility. Future extensive randomized studies are required to prove our associations between endometrial polyps and infertility.

Keywords: infertility, endometrial polyps

Deep endometriosis: when do we operate?

Diana Soare, Andrei Manu, Cătălin Bogdan Coroleucă, Elvira Brătîlă

"Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

Background. We define deep endometriosis as the peritoneal invasion of endometrial tissue more than 5 mm in depth. Frequently affected areas include the rectovaginal septum, the rectus, the sigmoid colon, the urinary bladder and the ureters. Usual symptoms include cyclical or noncyclical abdominal pain, infertility, dysmenorrhea, dysuria and dyschezia. The diagnosis is obtained mainly clinical, laparoscopy being considered the gold standard, since the direct visualization of the lesions is possible, as well as correlation with the histopathological examination. The treatment can be medical or surgical. Setting aside the established indications for surgery – unresponsive pain and infertility, there are certain aspects that need to be considered more thoroughly, such as the progressiveness of the disease, as well as the functional impact on the affected organs. **Materials and method.** We present a systematic review in which we included articles regarding the surgical treatment of deep endometriosis and the right time when surgery is indicated. We will also present several cases of severe deep endometriosis, in order to emphasize the progressive character

of the disease and the consequences of late surgical treatment. **Results.** Endometriosis should be viewed as a chronic disease which affects the quality of life. Certain localizations of the disease can lead to irreversible damage, going as far as organ function loss. For example, parametrial nodules can obstruct the ureter, develop ureterohydronephrosis and lead to kidney failure. Intestinal endometriosis can cause bowel obstruction, as well as the destruction of the nervous plexus within the intestinal wall, that will lead to functional disturbances. The goal of laparoscopic surgery in deep endometriosis is to completely excise the lesions, reducing the risk of recurrence and reintervention as much as possible. **Conclusions.** The surgical treatment of deep endometriosis is a challenging task. The failure of treatment is correlated with the surgeon's experience, case complexity and the anatomical localization of the disease. Endometriosis is a chronic disease and the goal of surgery is to stop the lesional progression and to restore the normal anatomy and function.

Keywords: deep endometriosis, surgical treatment, laparoscopy

Impact of endometriosis on women's quality of life

Oana Toader^{1,2}, Alexandra Olaru^{1,2}, Mădălina Mârza¹, Ramona Dragomir^{1,2}, Ramona Mircea-Vicol^{1,2}, Nicolae Suci^{1,2}

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, "Gheorghe Polizu" Clinical Hospital, "Alessandrescu-Rusescu" National Institute for Mother and Child Health, Bucharest, Romania

Introduction. Endometriosis is one of the most common gynecological diseases and affects approximately 10% of women of reproductive age. The most common clinical signs of endometriosis are menstrual disorders, chronic pelvic pain, dysmenorrhea, dyspareunia and infertility. The symptoms of endometriosis often affect the psychological state and also the women's socio-familial behavior. For this reason, endometriosis is considered a disabling condition that can significantly compromise social relations, sexuality and the quality of life. **Materials and method.** A review of the literature on the impact of endometriosis on women's quality of life has been carried out. The strategy involved the use of keywords such as "endometriosis", "anxiety", "depression" and "chronic pelvic pain", with the selection of articles and the narrative description of the data obtained. **Results.** The psychological factors play an important role in determining the severity of symptoms, and women suffering from endometriosis report high

levels of anxiety, depression and other psychiatric disorders. In addition, endometriosis is one of the most important causes of chronic pelvic pain. Several studies have highlighted the influence of chronic pelvic pain on the quality of life of women with endometriosis and their psychological well-being. High levels of anxiety and depression have been shown to increase the severity of pain. In addition, women with endometriosis report significantly more sexual dysfunction compared to healthy women. **Conclusions.** The negative impact of endometriosis on women's quality of life has been widely demonstrated by the literature, along with the fact that the presence and severity of pelvic pain are associated with anxiety and depression. An individualized, couple-centered approach, that integrates psychosexual and medical management for endometriosis, is considered optimal.

Keywords: endometriosis, chronic pelvic pain, anxiety, depression



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Implications of human papillomavirus infection in infertility

Dragoş Albu^{1,2,3}, Alice Albu^{1,2,3}

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. ARTHOPE Bucharest, Romania

3. Department of Maternal-Fetal and Reproductive Medicine, MedLife, Bucharest, Romania

Introduction/objective. Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide. Reproductive function and pregnancy could be affected by HPV infection. The presence of HPV was reported in semen, and chronic viral infection determines the inflammation of low urethra, which provokes infertility. HPV in sperm was associated with miscarriage. Regarding fertility, this infection has also a negative impact in women. **Methodology.** Articles published in Web of Science Core Collection databases were reviewed. Only articles published in English until April 2020 were included. The research was performed using the following keywords: "HPV infection", "infertility", "semen". **Results.** In his study on 70 infertile men, Mohimi found a 11.4% prevalence of HPV infection. In men with HPV infection, sperm motility was lower and sperm morphol-

ogy was poorer than in control group. In his study on 729 infertile men, Boeri found a prevalence of 15.5% for HPV infection. The semen in HPV patients had a higher DNA fragmentation and poorer reproductive outcome. HPV infection during treatment for *in vitro* fertilization (IVF) or intrauterine insemination (IUI) was associated with poorer outcome. Spandorfer found a 50% lower pregnancy rate in IVF for women with HPV infection. Infected spermatozoa could act as a carrier of viral genome in oocyte during conception. HPV infection could alter the development of the embryo, especially in two cell phases. **Conclusions.** A multidisciplinary approach of infertile couple affected by HPV infection is very important, in order to improve not only the reproductive outcome, but also the overall health.

Keywords: infertility, HPV, semen

Impact of HPV infection on cervix transformation zones in young patients

Elena-Iuliana-Anamaria Berbecaru¹, Anca-Maria Istrate-Ofițeru^{1,2,3}, D. Ruican¹, Cătălina Rănescu¹, Iuliana Alina Dica¹, Andreea Vochin¹, Rodica Daniela Nagy¹, G.L. Zorilă¹, D.G. Iliescu¹

1. Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania

2. Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania

3. Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

Introduction. There are many types of human papillomavirus, and 14 of these types are commonly associated with cervical cancer. Approximately 70% of the cervical cancers and preneoplastic lesions are caused by types 16 and 18. Preneoplastic cervical lesions can be treated, and HPV infection can disappear under the action of the immune system. Persistent infections can progress to neoplastic lesions. **Materials, method and results.** This is a retrospective study, conducted in the period 2018-2019. This study included a group of 30 young patients, aged 17-29 years old. All the patients included in this study had cytological and colposcopic changes of the cervix and HPV HR+ genotyping. Some of the patients complained of vaginal bleeding after sexual intercourse, leukorrhea and vaginal discomfort, but most of them were asymptomatic and were diagnosed with HPV during a screening exam. For the patients with low-grade lesions on the cytological exam or colposcopy, it was decided to apply local treatments and a follow-up after six months. For the patients with high-grade lesions, we performed an excision of the cervical

lesions. The excised fragments were sent to the anatomic pathology department for microscopic study. Using the immunohistochemical study, we proved the presence of HPV in the excised tissue (positive anti-p16 antibody) and an increased degree of intraepithelial cell proliferation (CIN1-positive reaction to anti-Ki67 antibody in the basal layer, CIN2-positive reaction in the basal and intermediate layers, CIN3-positive reaction in the basal, intermediate and superficial layer). Seventeen patients presented high-grade lesions on the microscopic examination for the excised tissue. **Conclusions.** Untreated HPV infection leads to the transformation of normal cervical cells into premalignant and later malignant cells. These lesions were identified by histological and immunohistochemical studies that proved the degree of the intraepithelial lesions, by the presence of cells in the proliferation phase. The influence of HPV infection, demonstrated immunohistochemically, highlighted the prognosis and the evolution of the patients.

Keywords: human papillomavirus, colposcopy, microscopy

Means of increasing HPV vaccine adherence

Mihaela Boț, Aida Petca, Ioana Calo, Andreea Borislavschi, Mihaela Ichim, Radu Vlădăreanu

Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest; "Elias" University Emergency Hospital, Bucharest, Romania

Human papillomavirus can lead to cancer in both men and women. Almost all HPV-related cancers can be prevented by HPV vaccination (99%). HPV vaccines are recommended for adolescents between the ages of 11 and 14 years old, but adherence remains suboptimal and many adolescents do not receive the vaccine. A few strategies to ensure that many teens get vaccinated include using vaccination information systems and sending reminders to patients by their general practitioner. Educational interventions aimed at advising parents and adolescents to increase vaccine

coverage must become a priority. Clearly, alternative approaches to increasing HPV vaccination are urgently needed. We, as gynecologists, ought to give counsel to adolescents' mothers during their annual gynecological consultation. The aim is to improve, among parents, one by one, the level of knowledge on the effectiveness and efficiency of the vaccine, if we want to promote favorable attitudes, intentions and behaviors towards HPV vaccination.

Keywords: HPV, anti-HPV vaccine, education, counseling

The influence of vaginal pH on the progression of HPV lesions

Anca Burnei^{1,2}, Andra Lorentz¹, Theodora Mardale¹, Vlad Zamfirescu^{1,2}, Radu Vlădăreanu^{1,2}

1. "Elias" University Emergency Hospital, Bucharest, Romania

2. Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Cervical cancer is the most common malignancy in the gynecological field, with the highest death rate. Most cervical cancers are diagnosed at the stage of intraepithelial neoplasia (CIN), being caused by the HPV infection. In general, the body has the ability to heal spontaneously following infection with various HPV viral strains. Under certain conditions, pathology or exogenous factors may influence the persistence of the infection and the further progression to cervical injury and cancer. Several factors that would influence the change in vaginal pH and therefore alter the immune function were evaluated. These factors were mostly represented by vaginitis with various infectious agents, vaginal candidiasis, *Trichomonas vaginalis* infection, oral contraceptive treatments, age and pregnancy. Bacterial vaginosis is characterized by the imbalance of normal vaginal flora with the increase of vaginal pH above 4.5. In relation to HPV infection, it was as-

sumed a possible correlation of the fact that the normal flora, mainly composed of lactobacilli, would produce hydrogen peroxide as a defense mechanism of tissues against pathogenic conditions. If the normal microflora of lactobacilli is destroyed for various reasons, the local defense is low, creating a favorable ground for the persistence of HPV infection. The vaginal HPV infection is caused by some biological interaction between these factors, or both can occur in a certain group of females which present some risk factors that are still unknown. It is known that the presence of vaginitis can be associated with HPV infection – a strain with a high oncogenic risk. Additional molecular studies are needed to demonstrate the synergic interaction between viral factors represented by HPV strains and infectious or environmental factors.

Keywords: HPV, vaginal microflora, vaginitis, vaginal pH

Etiopathogenesis of premature birth in patients with HPV genital infection

Dragoș Crețoiu¹, Nicolae Bacalbașa¹, Ioan-Dumitru Suci², Nicolae Suci¹

1. Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Bucharest University Emergency Hospital, Romania

Objectives. Literature analysis of the influence of HPV genital infection on the pregnancy outcome. **Methodology.** A series of studies and literature data were evaluated regarding the risk of human papillomavirus infection in pregnancy and the implication in premature birth. **Results.** Six studies were included in the paper. HPV alone or surgical interventions due to HPV infection were analyzed as a risk factor in the outcome of the pregnancy. The results of the studies varied. The three studies that analyzed HPV-related disease of the cervix concluded that HPV is incrimi-

nated in poor pregnancy outcome. Three studies of the PPRM and HPV had different results. One study showed that HPV is not involved in pregnancy outcome, while the other two studies offered data, concluding that HPV is involved in premature birth. **Conclusions.** Research on the HPV involvement in premature birth offer precious data that may lead to new research area in the near future, with valuable results and influence in the pregnancy outcome.

Keywords: HPV, genital infection, pregnancy outcome

Consistencies and discrepancies in preneoplastic cervical lesions

Corina Grigoriu

Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy; Bucharest University Emergency Hospital, Romania

Introduction. The goal of cervical cancer screening is to rapidly detect and treat severe preneoplastic lesions, which would otherwise have the real potential to develop a neoplastic lesion. The diagnostic approach includes individualized algorithms, and the treatment consists in removing the suspicious lesion within healthy margins, with confirmation by histopathological examination. **Materials and method.** We analyzed the diagnostic methods that we use and the degree of correlation with the results of the histopathological and immunohistopathological examination. We insist on frequent situations in gynecological practice, which move away from the ideal cases of perfect concordance between cytology, HPV genotyping, immunocytology, colposcopy and histopathological examination. **Results.** From the case studies focused on the preneoplastic pathology of the cervix, we note:

- Patients with repeated negative cytology, but with a rich inflammatory background, who on opportunistic examinations receive HPV HR16, 18 or 45

positive results; positive colposcopic examination, major grade histopathological result (CIN 2+).

- Patients with repeated ASCUS cytological results, HPV HR negative, suspicious colposcopic lesions, with either minor or major histopathological results.
- Young patients without positive cytology, but with HPV HR positive, in which the interventional attitude is untimely taken, the histopathological result being negative.
- Young patients with AGC cytological results, in whom colposcopy and histopathological examination confirm a high-grade result for a squamous, not glandular lesion.

Conclusions. We advocate for a more personalized attitude, which takes into account individual risk factors (onset of sexual life, number of sexual partners, smoking, other associated persistent genital infections). Consulting recent ASCCP guidelines, with an extremely pragmatic approach, can be very useful in this regard.

Keywords: consistencies, discrepancies, preneoplastic cervical lesions

Giant condyloma acuminatum – case presentation

Anca-Maria Istrate-Ofițeru^{1,2,3}, D. Dițescu⁴, Elena-Iuliana-Anamaria Berbecaru¹, L.M. Dîră¹, Roxana Cristina Drăgușin¹, Maria Cristina Comănescu¹, Ileana Drocaș¹, Alina Iuliana Dica¹, Andreea Vochin¹, G.L. Zorilă¹

1. Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania

2. Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania

3. Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

4. "Constantin Brâncuși" University, Târgu-Jiu, Romania

Introduction. *Condyloma acuminatum* is a clinical manifestation of human papillomavirus infection. This pathology is characterized by the presence of fleshy, pigmented papules, located in the anogenital region. The most common types of HPV which cause these anogenital warts are HPV 6 and HPV 11. **Case report.** A 31-year-old patient, with a caesarean birth in the obstetrical history, came to the hospital's ambulatory service with several giant tumors/warts in the anorectal region. The tumors started to develop four years ago and have grown ever since. It was decided to apply the surgical treatment with the excision of these formations and to send the excised pieces to the pathological anatomy department. The histopathological result proved the presence of HPV infection (positive immunostaining with anti-p16 antibody), an increased degree of cell proliferation (intensive immunostaining with anti-Ki67 antibody), an abundant vascularization

of warts, and cauliflower-like formations (intense immunostaining with anti-cluster of differentiation 34 antibody). All of this proves the ability of the condylomatous tumors to grow and develop very fast. The negative reaction on the immunostaining with the anti-p53 antibody demonstrated the benign character of the tumors. **Conclusions.** The surgical treatment does not cure the HPV infection, but it does help improving the patients' quality of life. Histopathological and immunohistochemical examination helped us prove that the clinical development of the tumors was determined by the presence of HPV, and the accelerated development of warts was achieved from a large number of dividing cells, supported by an intense vascularization. The absence of oncoprotein p53 confirmed the benignity of cauliflower formations.

Keywords: anogenital region, human papillomavirus, surgical excision

The impact of age and HPV status on the prevalence of CIN3+ lesions in patients with HSIL and ASC-H cytology

Laura Leonte, Bianca Stanciu

"Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

The ASCCP 2019 guidelines stratifies the risk for a high-grade CIN3+ lesions, not only based on current screening test results, but also based on age and individual history. The aim of this study is to analyze the prevalence of CIN3+ lesions according to age and oncogeneity of the HPV genotypes in patients with HSIL and ASC-H cytological changes and to analyze the importance of colposcopy in the management of these cases. **Methodology.** The study includes a retrospective analysis performed on a group of 126 patients with HSIL and ASC-H cytology, who addressed the colposcopy department of the "Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, between January 2018 and February 2021, who were tested for HPV and in which a surgical electroexcision procedure was performed. **Results.** 64.3% of the 70 patients with

HSIL and 21.4% of the 56 patients with ASC-H had a CIN3+ lesion. The prevalence of CIN3+ lesions was inversely proportional to the age of the patients and was maximum (83%) in the group of patients with HSIL cytology and infection with HPV 16/18 genotypes. In most cases, these patients had major colposcopic changes. **Conclusions.** Age over 50 years old, infection with HPV 16/18 genotypes, HSIL cytology and the severity of colposcopic impression were important predictive factors in the diagnosis of CIN3+ lesions. The results of the study support the calculation of the risk for a CIN3+ lesion according to the ASCCP 2019. The colposcopic impression had a decisive role in the management of these patients.

Keywords: HSIL cytology, HPV genotype, CIN3+ lesion, age, colposcopic impression

HSIL management. Correlations between colposcopy and histopathological examination

Mihai Mitran^{1,2}, Sorin Puia¹, Maria Olinca^{1,2}, Anca Potecă^{1,2}, Octavia Velicu^{2,3}, Roberta Ciobanu^{1,4}, Elvira Brătîlă^{1,2}

1. "Prof. Dr. Panait Sirbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

3. Medical Center for Diagnosis and Outpatient Treatment, Ministry of Justice, Bucharest, Romania

4. University of Medicine and Pharmacy of Craiova, Romania

High-grade squamous intraepithelial lesion (HSIL) includes the entities formerly called intraepithelial cervical neoplasia (CIN 2, CIN3), moderate and severe dysplasia, and *in situ* carcinoma. Although not all high-grade lesions will progress to cancer, HSIL is considered a preneoplastic lesion. The aim of our study was to compare colposcopy changes associated with the diagnosis of HSIL (high-grade squamous cervical lesion) cytologically and histologically confirmed and the role of the

interprofessional team in the prompt evaluation and management of these lesions. We evaluated cytological/histological diagnoses of HSIL and colposcopic diagnostic elements. The cytological and histological diagnoses were reported according to the Bethesda system. Out of the total of 1180 PAPS collected in 2020, a number of 27 presented HSIL results, these being the ones evaluated in the present paper.

Keywords: HSIL, colposcopy, cervical dysplasia

Conceptual shift in cervical cancer screening: from cytology to biomarkers

Șerban Nastasia, Ana-Cătălina Savu, Anca Angela Simionescu, Anca Popa, Manuela Cristina Russu

Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

By detecting abnormal cells, cervical cytology or the Babeș-Papanicolaou smear proved to be an effective cervical cancer screening tool, although it has a rather low sensibility. The recognition of the link between sexual activity and cervical cancer led to the idea of a sexually transmitted pathogen as a cause of cervical cancer. Persistent HPV infection is the trigger for almost all cervical cancers, allowing the development of new diagnostic and triage tools, in the form of biomarkers. The most important viral biomarker is HPV DNA, already in use for primary screening, triage or post-treatment

follow-up. E6/E7 mRNA and viral methylation are appropriate methods for identifying persistent HPV infections. Among cellular biomarkers, dual staining of p16INK4a/ Ki-67 on cytology reveals the presence of a CIN2+ lesion. On the other hand, the absence of E4 is a strong proof of a transforming HPV infection, making these biomarkers strong candidates for the screening of pathological specimens. Newer technologies include the detection of the amplification of the TERC gene, which plays a role in carcinogenesis and microRNAs.

Keywords: HPV, biomarker, cervical cancer screening

HPV-induced alterations in the squamous epithelium – lesions in the ENT and genital area

Maria Olinca^{1,2}, Maria Cristina Comănescu³, Loredana Mitran⁴

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. "Prof. Dr. Panait Sirbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

3. University of Medicine and Pharmacy of Craiova, Romania

4. ENT Department, "Elias" University Emergency Hospital, Bucharest, Romania

Human papillomaviruses have been the subject of numerous studies related to cervical cancer. But the tropism of these viruses for the squamous epithelium does not stop at the cervical level. Histologically similar lesions can be identified in other epithelia, including those in the ENT sphere. Although HPV-induced squamous cell carcinomas are not as frequent as the

cervical ones, when compared to the non-HPV-induced oral carcinomas, they have different clinical and phenotypic features and have a better prognosis. Also, in these cases, the possibility of prevention by vaccination is discussed.

Keywords: HPV, squamous epithelium, squamous cell carcinoma

Cytohistological correlations in HPV infection

Maria Olinca^{1,2}, Anca Potecă^{1,2}, Elvira Brătîlă^{1,2}, Loredana Mitran³, Mihai Mitran^{1,2}

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. "Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

3. ENT Department, "Elias" University Emergency Hospital, Bucharest, Romania

Cervical carcinomas can be prevented by detecting and treating precancerous lesions early. Although the cytological screening has decreased the incidence worldwide, the results obtained must be integrated in a clinical context in order to avoid false-positive diagnoses. Persistent infection with high-grade HPV is the leading cause of preneoplastic and neoplastic lesions. Although the Babeş-Papanicolaou cytological examination, performed both conventionally and liquid-based, is the

most efficient method in terms of quality/price ratio, and the histopathological examination is often considered the gold standard, in some cases there are inconsistencies between the two. In our study, we aimed to retrospectively evaluate Babeş-Papanicolaou smears and post-biopsy results in order to determine the incidence of false-positive and false-negative cases.

Keywords: Babeş-Papanicolaou smear, cervical biopsy, squamous neoplasia

Dermoscopic findings and HPV genotypes of genital keratotic lesions: bowenoid papulosis, seborrheic keratosis and *condyloma acuminatum*

Florica Şandru¹, Adelina Popa², Mihai Cristian Dumitraşcu³

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest; Department of Dermatology, "Elias" University Emergency Hospital, Bucharest, Romania

2. Department of Dermatology, "Elias" University Emergency Hospital, Bucharest, Romania

3. Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy; Bucharest University Emergency Hospital, Romania

Introduction. Gynecologists and dermatologists often encounter keratotic lesions in the genital area. Although making a clear diagnosis can be difficult, it is important for the treatment and prognosis closely related to the patient's quality of life. Dermoscopy has proven to be a useful, noninvasive tool. However, there is still a lack of dermoscopic data comparing bowenoid papulosis (BP), seborrheic keratosis (SK) and *condyloma acuminatum* (CA). More than 40 human papillomaviruses genotypes infect the genital area and manifest as various intraepithelial neoplasms. **Methodology.** This paper is realized to describe the distinctive dermoscopic features and HPV genotype distribution of BP, genital SK and CA. **Results.** Dermoscopically, BP presents glomerular vessels, CA presents hairpin vessels and SK is the least

vascular-patterned disease. SK shows cerebriform and CA has a knob-like or finger-like appearance and a whitish halo. BP and CA have positive results at the HPV DNA detection, but studies have shown that more than half of SK have positive HPV results. For the high-risk genotype, mainly HPV 16, BP shows the highest detection rate, and for the low-risk genotype, mainly HPV 6 and HPV 11, CA presented the highest detection rate.

Conclusions. Dermoscopy can be useful for differentiating the entity of genital keratotic lesions ahead of an invasive method and a physician should consider the morphologic plasticity of HPV-related keratosis in the genital area or the genital wart in the expanded concept.

Keywords: dermoscopy, bowenoid papulosis, seborrheic keratosis, *condyloma acuminatum*

HPV infection in pregnancy and prematurity

Oana Toader^{1,2}, Alexandra Olaru^{1,2}, Mădălina Mârza¹, Ramona Dragomir^{1,2}, Ramona Mircea-Vicol^{1,2}, N. Suci^{1,2}

1. Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, "Gheorghe Polizu" Clinical Hospital, "Alessandrescu-Rusescu" National Institute for Mother and Child Health, Bucharest, Romania

Introduction. Epidemiologically reassessed, human papillomaviruses (HPVs), especially oncogenic genotypes (HPVhr), contacted by both partners in pre-conception and/or periconception, require the effective management of the possible risks of maternal-fetal complications and negative pregnancy outcomes. In recent years, multiple studies have evaluated the possible link between HPV infection and prematurity. Prematurity is one of the greatest challenges for obstetrics, both through increased incidence, at least 15 million babies being born preterm every year, and through the impact it has. The objectives of this paper were the review of the data on the HPVs etiology of prematurity in pregnant women, as well as the related maternal-fetal medical consequences. **Materials and method.** A review of the literature was carried out regarding the impact of HPV infection in pregnancy and the link between the presence of this infection and prematurity. The strategy involved the use of keywords such as "HPV infection", "high-risk HPV", "prematurity" and "pregnancy compli-

cations", with article selection and narrative description of the data obtained. **Results.** Simultaneously with the oncogenic effect on the female genital tract, the evolutions of HPVs infected pregnancies, especially HPVhr, are explored. The prevalence of HPVs detection in cervical and/or placental sites in pregnant women with complications and negative pregnancy outcomes varies between 2% and 70.4%. The prevalence of cervical HPVs in pregnant women varies between 15.9% and 67.1% in cases completed with preterm birth and between 18% and 27.3% in cases of preterm rupture of membrane. The prevalence of placental infection with HPVs varies between 18% and 50% in pregnancies completed with preterm birth. **Conclusions.** Gestational HPVs, especially HPVhr, induce a high risk of prematurity with related maternal and fetal medical consequences and requires routine preconceptions and/or periconception investigations of HPV for both partners.

Keywords: prematurity, HPV infection, high-risk HPV, pregnancy

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