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REVIEWS

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REVIEWS

REVIEW

A Modern View of the Polycystic Ovarian Syndrome

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Abstract

The polycystic ovarian syndrome (PCOS) is the most common endocrinopathy, which affects between 8 and 13% women of reproductive age.Its most common and disturbing features are hyperandrogenism and infertility. Due to its many implications, there is an utter need to improve the diagnosis and management of this pathology. It will help women improve their quality of life, fertility and prevent cardiovascular effects. The most important part of the management is the correct diagnosis. Specialists are trying to elaborate tighter and more specific criteria of diagnosis. Besides these disturbing features, one can not ignore the more important effects of PCOS: cardiovascular disease, diabetes mellitus, endometrial cancer and mental disorders (anxiety and depression)In order to prevent all these problems, the patients need constant guiding with a major change in lifestyle.

Key words: PCOS, hyperandrogenism, infertility, lifestyle.

Introduction

The polycystic ovarian syndrome (PCOS) is the most common endocrinopathy, which affects between 8 and 13% of the women of reproductive age [1].This complex pathology has many implications: reproductive, metabolic and psychologic [2]. Over the years, scientists have elaborated different methods of diagnosis and treatment but clinical practice is still inconsistent. Recently, articles have been published about women's disatissfaction with care and delayed diagnosis [3, 4]. The Rotterdam diagnostic criteria have been released in 2003 and since then, have been intensely used. Due to the complexity of the pathology, there is an obvious need for tighter criteria, in order to include the pacients who were previously undiagnosed. That is the reason why we started writing this paper, in order to offer a modern perpective of the polycystic ovarian syndrome to women all around the globe. This article's purpose is to facilitate

diagnosis of the polycystic ovarian syndrome and to avoid overdiagnosis in adolescents.

Rotterdam criteria include the following:

(1) ovulatory dysfunction – oligo/anovulation,

(2) clinical and/or biochemical hyperandrogenism,

(3) polycystic ovarian morphology in pelvic ultrasound.

In order to establish the diagnosis, the patient need to meet two out of three criteria. Other pathologies must be excluded, such as: congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome, thyroid dysfunction (thyroid stimulating hormone) and hyperprolactinemia (prolactin) [1, 5]. Beside the Rotterdam diagnostic criteria, the National Institute of Health suggested in 2012 four phenotypes of the polycystic ovarian syndrome:

(Phenotype A) hyperandrogenism, ovulatory dysfunction andpolycystic ovarian morphology in pelvic ultrasound

(Phenotype B) hyperandrogenism and ovulatory dysfunction

(Phenotype C) hyperandrogenism and polycystic ovarian morphology in pelvic ultrasound

(Phenotype D) ovulatory dysfunction andpolycystic ovarian morphology in pelvic ultrasound

This new classification is very useful, especially for infertility specialists. It helps them to personalize treatment and improve outcomes [6].

Contents

Ovulatory dysfunction

Irregular cycles and ovulatory dysfunction are common in adolescence and menopause and finding the right criteria for diagnosis can be challenging. Irregular cycles are physiologic in the first year post-menarche. During the second year, almost 50% of the cycles range between 21 - 45 days. Cycles can remain irregular until the fifth year. So it may be difficult to diferentiate between physiologic ovulatory dysfunction and PCOS in adolescents. They may experience primary amenorrhea until the age 15 or > 3 years after telarche. In PCOS adolescents, in the second year after menarche, cycles tend to be very short (< 21 days) or very long (> 45 days) [7]. In the third year, menstrual cycles appear < 21 days or > 35 days or < 8 cycles/year. These fluctuations last until perimenopause. If an adolescent presents with both hyperandrogenism and irregular cycles, there is no need to perform a pelvic ultrasound. The clinicians need to take into account the impact of the psychosocial and cultural factors at this age and find the optimal timing for assessment, diagnosis and treatment (if necessary). Even if the patient has regular cycles, the ovulatory dysfunction can still exist. Serum progesterone can be tested.

Biochemical hyperandrogenism

Hyperandrogenism is a key diagnostic feature of PCOS and assessment of biochemical hyperandrogenism can be challenging, due to different methods of testing, different assays and cost of high quality tests.Testing the androgen hormones is useful in patients with unclear or absent biochemical hyperandrogenism. The formula of Vermeulen et al. is often used, which includes calculated bioavailable testosterone and calculated free testosterone. Free androgen index is also commonly used (FAI – free androgen index = 100 x (total testosterone/SHBG) [8]. Dehydroepiandrosterone sulfate (DHEAS)and androstenedione are less relevant, but can be used if testing other hormones is not available [9]. In women on hormonal contraception, treatment must be stopped for three months or more for a correct diagnosis, due to the effects on sex hormone-binding globulin (SHBG) and

gonadotropines.As clinicians, we must always keep in mind differential diagnosis until final diagnosis.

Clinical hyperandrogenism

Signs and symptoms of hyperandrogenism are: acne, hirsutism and androgen-relating alopecia. There are available different assessment scales for alopecia and hirsutism, for example the visual Ludwig score and the visual assessment tool, the Ferriman Gallwey scale [10]. Taking into consideration the ethnic variations in vellus hair density, some women can overestimate hirsutism. This is the reason why we should only consider terminal hair (>5mm). In postmenopause, patients cand still have clinical hyperandrogenism, but if it appears de novo, we should exclude androgen secreting tumors [11].

Polycystic ovarian morphology in pelvis ultrasound

The ultrasound aspect should not be used as a part of diagnosis in those with a gynaecological age < 8 years (< 8 years after menarche), because of the commonly seen multifollicular aspect of the ovary in these early years. For diagnosis, we need more than 20 follicles per ovary between 2 - 9 mm and/or ovarian volume ≥ 10 ml [12].

Cardiovascular Risk

As formerly mentioned in the first part of the article, patients with polycystic ovarian syndrome most often have metabolic changes and high risk of cardiovascular diseases. This, mostly affects postmenopausal women, although cardiovascular diseases can develop even in the early stages of adult life. Thus, the recommendations are: periodic weight evaluation and BMI, best regarding waist circumference (at least once every 6 - 12 months), all women with PCOS should investigate the risk factors for cardiovascular diseases, considering a hypolipidic diet and assessing lipid profile for overweight and obese patients and blood pressure monitoring [13, 14].

Gestational diabetes, impaired glucose tolerance and diabetes mellitus

PCOS represents an important risk factor for gestational diabetes, impaired glucose tolerance and diabetes mellitus regardless of age, a risk that is soared by obesity [15]. Glycemic status (fasting glycemia and/or glycate hemoglobin – HbA1c) must be routinely monitored, from the first consultation, for all PCOS patients and then assessed at least once every 1 - 3 years, however, this recommendation can vary depending on the glycemic status and other risk factors for diabetes [16]. If the patient belongs to a high risk ethnic population (asians), has a high BMI (≥ 25 kg/m^2 or ≥ 23 kg/m^2 for asians), has a history of high fasting glycemia, impaired glucose tolerance or gestational diabetes, heredo-collateral history of diabetes mellitus or hypertension, it is recommended to conduct an oral-intake glucose tolerance test (OGTT) with 75 g of glucose [16, 17]. Considering the hyperglycemic risk in pregnancy and its associate comorbidities, it is recommended OGTT with 75 g of glucose for all patients planning pregnancy. If the test was not assessed preconceptional, this may be offered < 20 weeks, and if not sustained in this period, it is mandatory to perform it between 24 - 28 weeks [16, 17].

Endometrial cancer

PCOS patients have a 2 to 6 -fold higher risk to develop endometrial cancer, which usually appears before menopause [18, 19]. It is recommended to perform a transvaginal echography and endometrial biopsy for patients with PCOS or with history of PCOS and thickened

endometrium, with prolonged amenorrhea, vaginal bleeding or overweight [20]. Prevention of endometrial cancer is not yet clearly understood, but an accurate approach seems to be consisting of correct administration of combined oral contraceptives or progesterone therapy for patients with > 90-day menstrual cycles.

Quality of life, body image alteration, depression and axienty, eating disorders

A recent metaanalysis showed that PCOS patients have a higher risk of mental disorders, like depression and anxiety (36.6 vs 14.2% and 41.9 vs 8.5%, respectively) [21]. As a result, the AE-PCOS Society recommends screening for depression and anxiety form the first consultation. The majority of patients with PCOS present acne, hirsutism or obesity, all of these leading to body image alteration and low quality of life. When considering medication for psyhiatric disorders, caution is needed for adminitration of antidepressants and anxiolitics for obese patients. Usually, women with PCOS and obesity tend to have eating disorders, this is a reason why it is important for the clinician to identify this issue and guide the patient properly [24, 25]. These patients need support and counseling to cope with major life changes. They need a healthy life-style, consisting of diet (1200 - 1500 kcal/day) and physical activity. A 5 - 10% weight-loss in 6 months leads to significant improvement regarding android obesity, insulin resistance, fertility and quality of life.

Treatment in PCOS

Combined oral contraceptives (COC)

COC are indicated for PCOS patients with hyperandrogenism and/or irregular cycles. The international guidelines recommend low dose ethinyloestradiol (20 - 30 microgram) and natural estrogen preparations because of the thromboembolic risk. COC can be recommended also to adolescents with hyperandrogenism and/or irregular cycles. When prescribing COC, we should not forget to take into consideration the patients history, his family history and other risk factors, such as hyperlipidemia, BMI and hypertension [26].

Metformin

Metformin is an insulin sensitiser and has been used for seven decades in diabetes and for several decades in PCOS. There is a variability in recommendations across specialists. If lifestyle changing and COC are not sufficient, metformin can be added to the treatment. It can be administered also as an only treatment for PCOS [26]. Metformin can offer great benefit in patients with diabetes risk factors, impaired glucose tolerance and high risk ethnic groups. In obese patients undergoing and IVF procedure, metformin should be considered. In this case, the treatment should start with at least 8 weeks before ovum-pick up, in order to eliminate the risk of hyperstimulation ovarian syndrome, to improve pregnancy rates and diminish abortion rates. [27, 28]. It is recommended to start with a low dose (500 mg) and increase up to 1500 mg, depending on the patient's status. The most common adverse effects are the gastrointestinal effects, which are dose dependent and self-limiting. Even though metformin seems to be safe in the long term, concerns on B12 deficiency have been raised and more research is needed [29].

Antiandrogens

Cosmetic therapy and COC should be applied correctly for at least 6 months in any patient with hirsutism. In those patients, in which treatment is not efficient and those with androgenic alopecia, an antiandrogen can be added to the COC scheme. If there is a contraindication for

COC, the antiandrogen can still be administered [30 - 32].

Inositol

Inositol works as an insulin sensitiser but its efficiency remains unclear. There is a need for larger studies [33].

Ovulation induction agents - letrozole, gonadotropines, clomiphene citrate

Letrozole is the first line treatment for ovulation induction in patients with PCOS and anovulation. In case of failure, gonadotropines can be added, but we should counsel the patient on the multiple pregnancy risk and costs [34].If there is no other option (letrozole pr gonadotropines) clomiphen citrate can be used, but with caution, regarding the possible detrimental effects on the endometrium and cervical mucus [35].

Laparoscopy

Ovarian drilling is the last option for ovulation induction. The specialist must bear in mind the following: high costs, high intraoperative and postoperative risks in obese patients, risk of decreasing the ovarian reserve or even loss of ovarian function , periadnexal adhesion [36].

IVF

If ovulation induction treatment is not effective, specialists should opt for in vitro procedure. Regarding the stimulation protocol used, it is recommended the short protocol with antagonist GnRH and final oocyte maturation with GnRH agonist. The specialist should counsel the patients in order to adopt freeze-all strategy, in order to prevent hyperstimulation ovarian syndrome [36, 37]. Urinary or recombinant follicle stimulating hormone can be used for stimulation and luteinizing hormone treatment should be avoided [38, 39].

Conclusions

There is still a need for prospective randomized studies regarding PCOS, in order to make stronger recommendations. Even so, we consider that the information available for assessment and manangement of PCOS is useful. Nowadays, it is very important that we guide our treatment according to evidence-based medicine, and not to personal experience.

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REVIEW

A Severe Case of Folliculitis Decalvans

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Abstract
Folliculitis decalvans (FD) is an uncommon, chronic skin disease, characterized by cicatricial alopecia and follicular pustules. This condition affects men more often, and rarely occurs in children. The etiopathogenesis suggests that immunologic response to staphylococcal superantigens may play a role in FD. Treatment is necessary, and should be adapted to the clinical form and severity of the disease.

Key words: folliculitis decalvans, doxicycline, S. Aureus.

Introduction

Folliculitis decalvans (FD) is a rare, chronic, primary neutrophilic scarring alopecia, characterized by expanding patch of alopecia, with pustules. In some cases, it associates pain or pruritus [1]. The incidence in not exactly known, an it is estimated between 9% and 11% [2, 3]. FD occurs more often in men, and rarely affects children [4].

Etiopathogenesis of FD is still unclear. However, involvement of *S. aureus* has been accepted: not only its bacterian role, but also staphylococcal superantigens that bind to class II major histocompatability complex (MHC) proteins, causing nonspecific activation of T lymphocytes, resulting in release of cytokines and follicular destruction [5]. Other theories include: an autoimmune process, a genetically determined immune deficiency, pathogenic biofilms, and a congenital abnormality of follicular orifices [6 - 8].

Clinically, FD presents as multiple confluent plaques of cicatricial alopecia, with pustules, with/without inflammatory papules and sbsence of follicular orifices [9].

The diagnosis of FD is established by cicatricial hair loss and histologic evidence of a neutrophilic inflammatory infiltrate [10].

Management of patients with FD is important, because this scarring alopecia may lead to loss of all hair follicles. Treatment should always be started when the disease is active, and this means the presence of pustules, crusts, erythema, pruritus or pain, progressive scarring, or progressive hair loss. On the other hand, when this signs of inflammation do not exist any more, response to treatment is low [11].

Case report

We present the case of a 48 years old man, who referred to our Dermatology Clinic for the evaluation of a multiple scarring, confluent plaques, at level of the scalp, accompanied by pruritus and pain, in evolution for 1 year. The patient was treated with several topic antibiotics, but the disease continued to progress. Family history and medical history were unremarkable. Except the skin lesions, physical exam revealed no other abnormal findings.

On clinical exam of the skin we found: multiple erythematous, scarring, confluent plaques, with variable diameter, with crusts and pustules, at level of the scalp (Fig. 1).

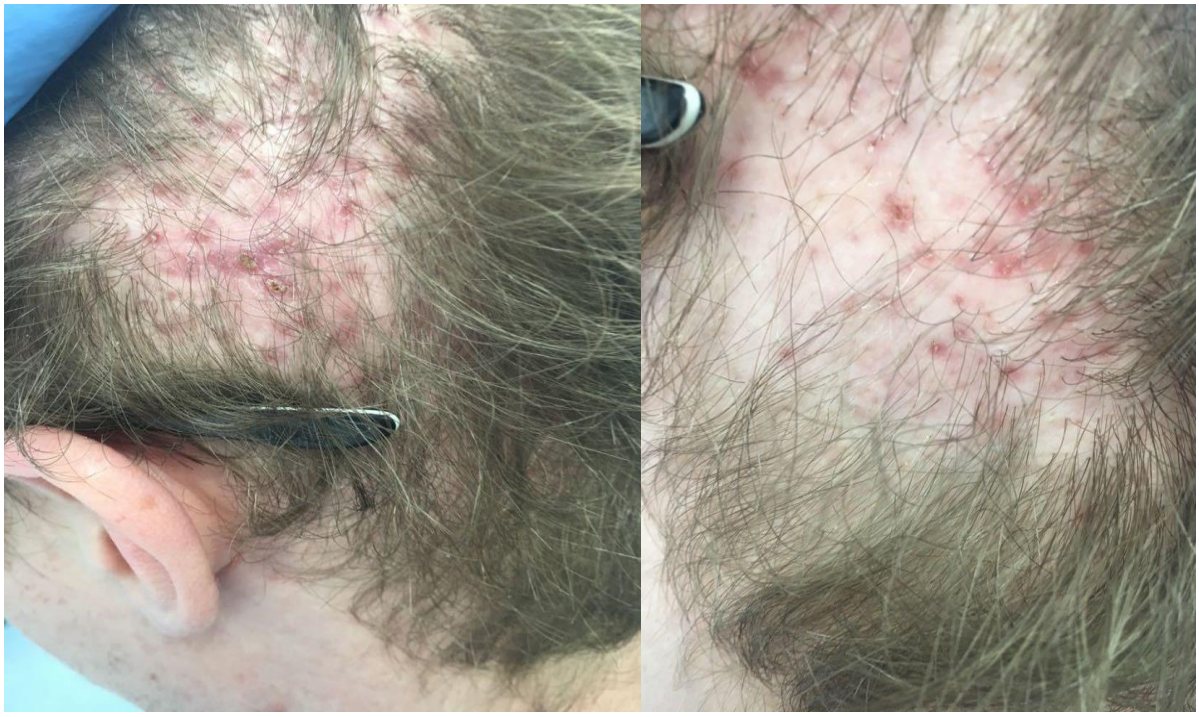

Fig 1- plaque of cicatricial alopecia, with pustules and crusts

Routine blood tests were normal.

We performed dermoscopy, which revealed: absence of follicular ostia, perifollicular erythema, perifollicular epidermal hyperplasia observed in a starburst pattern, hair diameter diversity, and large, follicular pustules.

We suspected FD, and for a diagnostic of certainty, we prelevated a skin biopsy, from the periphery of a cicatricial plaque, with

histopathological examination: dense, perifollicular inflammation of the upper portion of follicles, epithelial destruction, lymphocytic inflammation. The histopathological examination sustained the clinical aspect: FD.

Corroborating the clinical, paraclinical data, and histopathological examination, we set the final diagnosis of FD.

The management of a patient with FD is challenging. We initiated systemic therapy with oral antibiotic: Doxycycline 100 mg/day. Also, because symptoms (pain, pruritus) were very disturbing, we recommanded dermatocorticoids. Local, we apllied disinfectant solution and antiseptic shampoons. The treatment was well tolarated.

The patient presented to the control, four weeks after discharge. Evolution of the disease was favorable, as the palques did not extend any more. Also, the patient denied any symptoms.

Discussions

Diagnosis of FD should include several criteria: one or more confluent areas of scarring alopecia on the scalp, absence of follicular ostia in areas of alopecia, perifollicular scale extending onto the hair shaft and tufting of hair shafts [12].

Differential diagnosis of FD includes: dissecting cellulitis of the scalp, acne keloidalis nuchae, erosive pustular dermatosis of the scalp, tinea capitis, lichen planopilaris,
discoid lupus erythematosus, central centrifugal cicatricial alopecia [9].

Treatment of FD is difficult, and is adapted to the clinical, severity and extension of the condition. Because this skin disease is a cicatricial one, the therapy should be started as soon as possible. First-line therapy is represented by tetracyclines: 50 to 100 mg of doxycycline or minocycline given twice daily. Its beneficial effects are observed in one to two months. In case of severe symptomes, one of the options would be triamcinolone acetonide for injections in the affected area, administrated in several sessions, at in interval of four to six weeks or longer. Local, a high-potency topical corticosteroid is one of the options. In acute episodes, systemic glucocorticoids may be useful [13]. However, because of their multiple side-effects, are not recommanded in long-term therapy. In case of failure of initial treatment, the alternatives include: rifampin, clindamycin, or oral isotretinoin [11].

Conclusions

In conclusion, diagnosis and management of FD are challenging. Because this skin condition is evolving with alopecia, diagnosis should be established and therapy should be started as soon as possible. Also, follow-up of patients with FD is important, due to the chronic course of the disease.

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REVIEW

Alloplastic Breast Reconstruction

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Abstract

Immediate breast reconstruction is a surgical technique that involves placing an implant or expander in the same operation with the mastectomy intervention. Thus, the remaining flaps are viable, fresh and the remaining space can be filled with an implant. Patient satisfaction is increased, thus avoiding the psychological shock of not having a breast and they support better the following interventions.

The aim of this paper is to review and find in the current literature the indications and technique of immediate breast reconstruction in order to help surgeons to choose and perform the most appropriate breast reconstruction method. We have also researched in the literature the rates of complications that have arisen, especially in the case of subsequent radiotherapy.

Multidisciplinary approach of these cases presented the key to success, oncological safety is the main concern, then the reconstruction must respect the patient's requirements and ensure the best aesthetic result.

Key words: immediate breast reconstruction, mastectomy, surgical technique.

Introduction

Breast cancer is the most common malignancy in female population [1]. In the current era, the detection of breast cancer in a low stage has increased considerably which has led to an increase in the number of mastectomies and immediate or delayed reconstruction surgeries [2, 3]. Immediate breast reconstruction (IBR) is designed to increase patient quality of life, the surgery should be proposed for patients about to undergo mastectomy being part of the breast cancer treatment protocol. The purpose of intervention is to protect the integrity and psychological state of the patient [4].

Breast reconstruction can be allogeneic (with a silicone implant or expander), autologous (with loco-regional or free flaps) or a combination of the two. Reconstruction may be performed at the same time as mastectomy as a single-stage intervention or may be delayed as a two-stage intervention

[5]. It is better to consider also the possibility of performing a second surgery that may be necessary for: reconstruction of the areolo-nipple complex, symmetrisation of the contralateral breast or revision of the scar [6].

The aim of this paper is to review and find in the current literature the indications and technique of immediate breast reconstruction in order to help surgeons to choose and perform the most appropriate breast reconstruction method.

Indication

Immediate breast reconstruction uses an implant or expander to shape the breast in a single intervention using the remaining flaps of the mastectomy without affecting the local vascularization. Preoperatively, parameters such as trunk skin elasticity, soft tissue characteristics and body proportions are evaluated [7]. Intraoperatively, it was found that the flaps remaining for the mastectomy should be at least one cm thick with good vascularization [8].

Young and thin women with small or medium breast represent the ideal candidates for the IBR [9]. This technique is intended for breast cancer cases in stage I or in selected cases in stage II [10]. When the contralateral breast has a degree of ptosis, ADM (Acellular Dermal Matrix) can be used to determine a similar appearance [11]. This can increase the muscular plane, stabilize the inframammary fold and improve the appearance of the lower pole [12]. An expander can be used when the tissues require modification but it must be replaced later with a definitive implant. It has been shown that this causes a higher rate of complications later [11].

According to the European Society of Breast Cancer Specialists more than 40% of patients benefit from immediate breast reconstruction after mastectomy [13].

Surgical technique

The immediate reconstruction is usually performed after surgical operation like skin-sparing mastectomy or nipple-sparing mastectomy. After the mastectomy is completed, the surgeon checks the viability of the remaining flaps, the color of the skin, the temperature, the capillary refill and the skin bleeding [14]. At this time, the plastic surgeon has several surgical options. The implant pocket can be created either in the submuscular plane or in the subcutaneous plane using materials such as: ADMs, autografts or synthetic meshes [15].

Placing the implant in the prepectoral position presents the great advantage of leaving the pectoral muscle untouched, which means an increased tolerance of patients to this intervention. This eliminates the deformity animation when moving the arms and chest. It should be noted that this technique requires the implant to be wrapped with a mesh like ADM that acts as a vascular regenerative tissue and allows stabilization of the breast reconstruction. Sometimes other interventions are needed to transfer fat to the upper pole of the breast because the implant may be visible due to its superficial position [16]. Placing the implant in a retropectoral position is similar to breast augmentation for cosmetic purposes but the lower pole should be covered with a mesh like ADM to stabilize its position and give it a better aesthetic appearance. In this case covering of the lower pole with the serratus fascia could also be used, but the appearance is not so natural.

According to studies that observe complication rates for both techniques, there is no significant differences in terms of complications, so the choice of a reconstruction technique depends on the patient's preferences and the surgeon's experience [17].

Discussions

Nowadays advanced plastic surgery techniques allow breast reconstruction to be performed more easily and to achieve better aesthetic results. Breast reconstruction performed in a single stage is an appealing option when anatomical considerations and allow its oncology. There was considerably increased psychological satisfaction with breast reconstruction in one stage compared with the two stages reconstruction when studies compared these techniques, which encourages both patients and surgeons to attempt single-stage reconstruction [18].

Careful selection of patients who can benefit from immediate reconstruction is mandatory. First, the primary considerations are oncological, aesthetic considerations being subsequently analyzed.

Detection of the positive sentinel lymph node prior to breast resection or reconstruction intervention guides the operative plan because it may reduce further complications or implant loss. Patients in whom the sentinel lymph node was positively identified have an increased risk of complications following immediate breast reconstruction and are potential for postmastectomy radiotherapy [19].

Another aspect that need to be planned ahead is the post-mastectomy radiation therapy because it determine significant changes in tissues and presents an increased risk of complications. A study in Sweden that included 725 patients in four hospitals showed a 28% risk of failure to five years in suffering radiotherapy group vs. 10% in the group without radiotherapy [20]. Also, a risk of implant removal of 26% vs 8.3% and of infection 20% vs 2.6% has been reported in patients who have undergone radiotherapy compared to non-irradiated patients [21]. Other long-term complications that have been reported are pain, deformity of the breast and capsular contracture [22].

Taking all these aspects into consideration, it has been found that an immediate reconstruction using an expander followed by radiation and subsequent autologous reconstruction is an option with high success rate [23]. Such a reconstruction has a lower rate of long-term complications, but it is an elaborate surgery that requires a complex and experienced surgical team [24].

Whenever we consider the use of an implant either as a therapeutic or cosmetic option, we must inform the patient about the possibility of a cancer associated with the implant. Breast implant associated anaplastic large cell lymphoma is a type of lymphoma detected in the implant capsule. Is associated with the persistence of a seroma in the breast, the palpation of a tumoral mass or a capsular contraction [25]. The occurrence of this disease has been observed so far in the case of textured implants, having as proposed mechanism the existence of a chronic inflammation determined by the existence of the implant [26]. The occurrence of another cancer after a mastectomy surgery can have a strong psychological impact on the patient, so it is important to carefully monitor these patients and report any symptoms.

The greatest advantage of these techniques is of a psychological nature, because women undergoing mastectomy surgery have a fear of appearance and the absence of a breast can remind them constantly of the trauma they have gone through. Thus, immediate reconstruction helps women forget this episode faster and be more satisfied with their physical appearance.

Conclusions

Immediate breast reconstruction using an implant or expander is a surgical technique used more and more often due to its many advantages. Surgeons are considering this technique when oncological and anatomical considerations allow it. The existence of viable flaps is essential for the reconstruction and the placement of the implant in the retropectoral or prepectoral plane determines

good results that can satisfy the patients requirements.

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REVIEW

An Updated Management of Uncomplicated Recurrent UTI in Women

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Abstract

Management of recurrent UTI is a very topical subject due to the high prevalence of the disease, its influence on the quality of life and the resulting social burden, as well as the increasing ecological adverse effects of the prolonged and repetitive antimicrobial therapy prescribed over the time. Sustained efforts should be made for a better understanding of the risk factors and the pathophysiology of the UTI recurrence, a precise diagnosis and a circumspect attitude regarding the antibiotic prescription. All the alternative therapies must be considered and the best treatment option should be chosen, providing maximum efficiency and minimal risks for the individual and also for the community.

Key words: urinary tract infections, management, antimicrobial therapy.

Introduction

This topic has been discussed very frequently in recent years due to the high prevalence of urinary tract infections (UTI) among women, their significant recurrence rate and, above all, due to the risks of classical therapy for these recurrences. Repetitive and/or prolonged antimicrobial therapy prescriptions produced increases in the rates of antimicrobial resistance, colonization with multidrug-resistance microorganisms ("collateral damage" phenomenon) and contribute to the uprising incidence of Clostridium difficile infection worldwide [1-4].

Definitions and prevalence

According to the recent published American Urological Association (AUA) guidelines, 60 percent of the feminine population experience an acute episode of low UTI (cystitis) in their lifetime [1, 5, 6]. Approximately one third of these patients are prone to another episode and 25-50 % of them may have the misfortune to experience multiple UTI episodes [6-8]. Recurrent UTI (rUTI) are defined as two or

more culture-proved episodes of UTI experienced in a six month period or as three or more UTI episodes within one year; the mandatory condition for the veracity of the definition is that the episodes are separate infections [9]. As for the "culture-proved" term, the newest guidelines admit that a threshold of over 10^5 CFU is needed for asymptomatic patients, but a value of over 10^2 CFU can be enough for patients with a strong clinical suspicion of UTI (characteristic UTI symptoms) [1,10].

Recurrence risk factors

The conditions that predispose to the recurrence of UTI are multiple: anatomical, microbial, behavioral and even genetic. *Anatomic conditions* such as structural urinary tract abnormalities causing obstructions, dysfunctional pelvic support for the bladder and urethra, uterus, vagina, and rectum resulting in any degree of prolapse, genital organs cysts and even a shorter urethral-anal distance can predispose to persistence or reappearance of UTI [11]. *Microbial factors virulence* are considered to be the most important link in the perpetuation of the rUTI. The normal lower urinary tract hosts a microbial community which is very important for the prevention of uropathogens colonization at this level [12]. Disruptions of the normal flora can cause bladder colonization produced by the intracellular progression and survival of the bacterial colonies [13]. This phenomenon appears very quickly after the ascension of the uropathogenic germs in the bladder - in a few hours; type 1 and type P pili are responsible for the persistence of the germs in the urothelium [14-16]. Several *behavioral habits* can influence the prevalence of rUTI. In premenopausal women the most common risk factors for the recurrence of UTI are sexual intercourse, the use of spermicides, diaphragm and/or oral contraceptives. Classic factors enounced to be involved in rUTI development are no longer accepted as certain: bath tub usage, wiping patterns, delayed bladder voiding [13,17]. For postmenopausal individuals the factors often implicated are low estrogen levels, urodynamic disruptions, constipation [13,18].

Some *genetic* polymorphisms are also associated with a higher risk for rUTI due to a decreased cell-mediated bladder defense capacity; toll-like receptors variations, cytokine polymorphisms or deficiencies are the substrate of the familial aggregation of frequent UTI episodes [13,19].

Modern treatment issues in rUTI

While antimicrobial therapy is recognized to be the most efficient method to treat rUTI, the threatening increase of antimicrobial resistance among uropathogens and the uprising incidence of Clostridium difficile infections worldwide has determined a more circumspect attitude regarding the first treatment option in UTI and the development of the antimicrobial stewardship program [1,6,20,21]. However, is very difficult for the physician to adhere to this program and not to prescribe broad-spectrum antibiotics for an extended period of time to a patient presenting with cystitis and a history of excruciating recurrences. However, it is important to know that aggressive treatment of UTI with the intention to eradicate germ colonization can lead to a higher incidence of antibiotic resistance, more frequent upper UTI episodes and to the "collateral damage" phenomenon. [1,6].

Taking into consideration all these issues, recent guidelines strongly recommend to use, as first-line therapy, nitrofurantion, trimethoprim-sulfametoxazol (TMP-SMX) or fosfomycin, chosen according to local resistance pattern. The duration of the treatment should be as short as reasonable, but no longer than seven days, even if we follow the bacterial culture results and we prescribe parenteral antibiotics (*table 1).* Prior to the treatment,

the clinician should perform the urinalysis, culture and sensitivity for each episode, in order to change antibiotic regimen if needed. [6, 22].

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Table 1. *Antimicrobial therapy indicated as first-line options for uncomplicated UTI episodes*

	Nitrofurantoin	**TMP–SMX**	**Fosfomycin**
Efficiency	88–93%	90–100%	83–91%
Spectrum	*E. coli, S. saprophyticus*	*Extended to all typical uropathogens*	*Vancomycin-resistant Enterococci, Extended spectrum beta-lactamase, Gram Negative Rods*
Collateral damage	No	Minimal	No
Administration	100 mg BID x 5days	800/160 mg BID X 3days	3 g single dose

Adapted after American Urological Association guidelines 2019 [6]

Second-line agents are cephalosporins and fluoroquinolones, both having several disadvantages (lack of efficiency, fungal infections, clostridium difficile or extended-spectrum beta-lactamase K pneumonia infections development for beta-lactams; QTc prolongation, aortic aneurism and tendon rupture risks for qiunolones) [1, 23, 24].

A different approach is recommended for asymptomatic rUTI. A positive urine culture in a patient with no symptoms does not require antimicrobial treatment and surveillance, except for the cases programmed for surgical interventions and those with Proteus mirabilis-induced struvite stone formation [6].

Repeated symptomatic UTI episodes defined as rUTI imposes the use of prophylaxis methods. After analyzing several databases, all the guidelines agreed that the most effective way to eradicate/lower the UTI episodes is the prolonged antimicrobial treatment [6, 21, 22]. There are moderate-to-strong recommendations for a low dose of antimicrobial agent prescribed in a single evening dose or three doses per week or even as an after-intercourse dose. The agents of choice are listed in table 2 and the duration of the treatment can vary between 3 - 12 months [25 - 31]. For women with frequent UTI episodes related to sexual activity the guidelines recommendations are for one single pre or post-coital antibiotic dose [6, 21, 22].

Table 2. *Antimicrobial prophylaxis in rUTI*

Antimicrobial agent	***Dose***	***Possible adverse effects***
Nitrofurantoin monohydrate macrocristals	50 - 100 mg/day	Pulmonary toxicity, hepatotoxicity, peripheral neuropathy; avoid in eldery and in CKD $\geq$ stage 4
TMP-SMX	40/200 mg daily or thrice weekly	Skin eruptions including Stevens-Johnson syndrome, gastrointestinal and hematologic disturbances
Cephalexin	125-250 mg daily	Fungal infection, increased INR
Fosfomycin	3 g every 10 days	Gastrointestinal disorders, vaginitis

Adapted after American Urological Association guideline 2019 [6]

The efficacy of antimicrobial prophylaxis is counterbalanced by many inconveniences. First of all, based on many years of RCT studies, the guidelines agreed that, after the antibiotic administration period, the prevalence of rUTI episodes returns to the pre-treatment level. [6, 21, 22]. Second, antibiotic resistance may develop and the possibility of selecting multidrug-resistant strains is considerable [32, 33]. Specific adverse effects of each antibiotic drug and the risk of intestinal flora disturbance are also important problems to take into consideration after long-term antimicrobial prophylaxis.

For all the reasons mentioned above, there is an increasing interest in replacing the antibiotic prophylaxis in rUTI with other alternatives. Scottish guidelines recommend cranberry products as the first-line option in the non-antimicrobial treatment for rUTI. Based on the properties of proanthocyanidins (PACs) to block type P pili of E Coli and K pneumonia, with beneficial reduced bacterial adhesion to the urothelium, cranberry products are able to reduce the recurrences after a first acute UTI episode [34, 35]. The use of standardized tablet formulation in high strength doses is advised and the lack of adverse effects is an important argument for this treatment. It also seems that the association of PAC to TMP-SMX treatment can reduce the resistance development in patients treated with a combination of the two [36].

United States guidelines for UTI advises the use of D-mannose for blocking the uropathogens adherence to the urothelium trough the action of type 1 pili, in a 2 grams per day dose, prescribed for 3 - 6 months and without any adverse effects [22].

Methenamine hippurate is an urinary antiseptic used in the 80's, experiencing a return of interest in the recent years; many studies in progress show encouraging results, especially in catheterized patients [37]. Another antiseptic alternative for catheter-associated UTIs is represented by methylene blue potentiated by potassium iodide [38].

Immunoactive therapy is a customary option to be tried, with oral OM-89 or injectable annihilated strains of uropathogen E Coli (UPEC) as the most important representatives, but effective just as longer as the treatment is ongoing [39, 40]. Scandinavian practitioners prescribe acupuncture, effective by improving micturition dynamics, in 4 weeks-long sessions, with a notably improvement of the UTI episodes prevalence [41 - 45].

Local therapies are also proposed for improving the quality of life and lowering the recurrences of UTI. While estrogens or lactobacillus used via intra-vaginal route are already accepted used options with arguable results, the newer method of intravesical hyaluronic acid once a week for 4 weeks consecutively plus chondroitin injections is much more promising [6, 46 - 48].

Conclusions

Although it is a pathology known from ancient times, UTI management still necessitates concerted efforts and sustained interest of medical researchers. Because of the rUTI increased prevalence and its effects on the quality of life, and due to the ecological adverse effects of the antimicrobial therapy utilized for its cure, it is necessary to develop new therapeutic strategies with increased efficiency and minimal risks.

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REVIEW

Erectile Disfunction after Radical Prostatectomy

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Abstract
Management of recurrent UTI is a very topical subject due to the high prevalence of the disease, its influence on the quality of life and the resulting social burden, as well as the increasing ecological adverse effects of the prolonged and repetitive antimicrobial therapy prescribed over the time. Sustained efforts should be made for a better understanding of the risk factors and the pathophysiology of the UTI recurrence, a precise diagnosis and a circumspect attitude regarding the antibiotic prescription. All the alternative therapies must be considered and the best treatment option should be chosen, providing maximum efficiency and minimal risks for the individual and also for the community.

Key words: urinary tract infections, management, antimicrobial therapy.

Introduction

Prostate cancer (PCa) is one of the most frequent cancer that appears in men all around the world and especially in Western European Countries, becoming in the last decades more commonly diagnosed in younger men [1]. In present, the therapeutic approach correlated with bigger patient survival rate has been demonstrated to be radical prostatectomy (RP) [2]. Although in the last years a lot of advances have been made in the development of minimally invasive surgical techniques and new information of the surgical anatomy of the prostate, erectile dysfunction (ED) after RP is still a frequent complication, ranging widely between 6% and 68%, that concerns both physician and the patient [3]. Anyway, the early time of diagnosis, evolution of new surgical approach and the use of robotic systems, the evolution of less invasive treatments such as brachytherapy, has increased patients expectancies about the survival rate and the life quality level after prostate cancer so postoperative ED should be right managed, giving importance to all factors that could influence the preservation of erectile function after surgery. In our opinion the important factors are preoperative evaluation of patient, operative techniques, implementing a ample plan for postoperative erectile disfunction management.

Preoperative arrangements

The preoperative evaluation of the patient for radical prostatectomy is the first mandatory step in avoidance postoperative erectile disfunction. The evaluation of the clinical and pathological characteristics of the disease is extremely important in the treatment decisions. Pursuant to European Association of Urology guidelines [4] nerve-sparing (NS) techniques are a secure surgical tactic in the majority of PCa patients [5], however NS techniques are contraindicated in patients with extracapsular extension (ECE), such as a biopsy Gleason score >7 and clinical stage T2c or T3 disease. Despite EAU clinical recommendations, a few clinical studies showed that in a cohort of patients with high-risk characteristics, bilateral NS was achievable in 70% of the cases [6]. Beside that around 50% of the reported cases recovered EF 2 years after surgery. Overall before performing a RP, comorbidities such as diabetes mellitus (DM), cardiovascular diseases, advanced patient age represent other important factors for erectile disfunction in the general population [7, 8]; that will influence negatively postoperative EF recovery after radical prostatectomy. So, Rabbani et al presented the influence of age on the erectile function recovery after surgery, showing rates of recovery of 70%, 40%, and 30% for patients below 60 years, 60-65, and above 65 years of age [9]. Also, studies showed that vascular risk factors, including hypercholesterolemia, hypertension, DM, cigarette smoking and coronary diseases emerged as independent predictors of altered EF recovery 30 months after surgery [10]. Briganti et al. also created a risk stratification tool involving preoperative EF measured with the International Index of Erectile Function scores, the Charlson Comorbidity Index as a substitute for general health status and patient's age; they revealed that the risk of post-radical prostatectomy erectile disfunction could be stratified into 3 groups of risk: low risk for ED, intermediate risk for ED and high risk for ED [11]. The 3-year erectile function recovery rates were 85%, 59%, and 37% for patients in the low-, intermediate-, and high-risk categories. In conclusion preoperative erectile function status was found to be a major predictor of post-radical prostatectomy erectile function recovery [12]. It was demonstrated that up to 50% of patients with a few manifestation of ED before surgery they develop postoperative ED [13]. For these reasons, a critical and complete examination of EF is a fundamental part of the preoperative patient evaluation [14].

Intraoperative management

1. Physiopathology of postoperative erectile dysfunction

Penile erection is characterized as a neurovascular event regulated by hormonal status and psychological factors, where both vascular and neuronal constituents are vital in the physiological pathway [15]. Neurotransmitters in charge for the relaxation of the smooth muscle in the arteries delivering the erectile tissue during sexual stimulation are triggered by the cavernous nerve (CN) terminals that provide parasympathetic innervation to the corpus cavernosum; these terminals come from the pelvic plexus that is placed in the fibro-fatty stratum between the rectum and bladder [16]. So, post-radical prostatectomy erectile disfunction has been described as arterogenic, venogenic, neurogenic or a combination there of usually related to injuries of CNs and the pelvic plexus like neuropraxia caused by traction, compression, and coagulation during the apical and lateral dissection of the prostate [12, 13]. This kind of injury makes Wallerian degeneration of the nerves heading to the denervation of the corpus cavernosum and to the loss of nocturnal erectile function, determining also hypoxia and fibrosis of the penis that lead to ED [17]. It has been assumed that the first

mechanism in charge for postoperative arterogenic erectile disfunction could be the section of the accessory pudendal arteries (APAs), arteries described at 75% of patients that may determine penile hypoxia individually of the CNs [18].

2.Surgical anatomy

In the last decades the surgical prostate anatomy has dramatically improved so this conducted to important changes in surgical techniques, having an important goal - achieving better postoperative functional results. So in the context of erectile function recovery, two central aspects must be considered: the anatomy of the NVBs and prostate vascular supply.

a) Neurovascular bundles

The nerve fibers devising from the pelvic plexus and innervating the corpus cavernosum are located postero-laterally to the seminal vesicles and get in touch with the margin of the bladder neck, running adjacent to their tips; making the dissection of the seminal vesicles during radical prostatectomy an important factor that reduce ED postoperative [43]. Near to the prostate, nerve bundles are distributed "spray-like" on the anterolateral and posterolateral surface of the gland [19]. Studies showed that these fibers going anteriorly in NVBs innervate the prostate and the levator ani muscle, while nerve bundles located posterolaterally stimulate the corpus cavernosum [16].

b) Prostate arterial source

The prostate vascularization can start from the gluteal-pudendal trunk in 30% of cases, from the obturator artery in 15 % of the cases and from the internal pudendal artery in 50% of cases. The principal bifurcations of the artery are represented by an anterior branch reaching the lateral side of the prostate to the prostate apex and a posterior bundle around the vas deferens and the seminal vesicles and reaching the prostate base. So it was demonstrated that preserving the anterior capsular prostate arteries which are responsible for ancillary penile blood supply is usually associated with EF recovery [20].

3.Outcomes after radical prostatectomy: surgical techniques

In the last two decades has been made multiple studies about the incidence of erectile disfunction post radical prostatectomy each of them presenting different results.The reported results have been mostly influence by the different measures and definition of erectile disfunction used in each study, the patient selection criteria, the surgical technique and the different postoperative protocols used over time giving a variability of EF outcomes reports. Studies showed that after ORP at a minimum of 12 months of follow-up the recovery of erectile function is between 31% and 86 % [21]; similarly, after laparoscopic RP (LRP) have been reported to oscilate from 42% to 76% and after RARP EF recovery rates were between 30% to 70%, 50% to 80%, 50% to 90%, and 60% to 95% at 3, 6, 12, and 24 months after surgery [22]. In conclusion the last studies submitted that regarding of EF recovery the robotic approach in comparison to the laparoscopic technique or open surgery is superior. Still, the lack of randomized clinical trials, the different surgeon's experience and personal skill are factors that will impede anyone to choose for the momenta gold-standard technique for radical prostatectomy [23 - 35].

Postoperative management

The postoperative management of the erectile disfunction is mainly based on penile rehabilitation using two important therapeutic tools: pharmaceutical treatment and penile protheses.

1. Pharmaceutical treatment

Radical prostatectomy is mostly associated with period of inactivity of the nerves controlling erectile function, that can affect erectile tissue oxygenation and damage the corpora cavernosa, making any chance of EF recovery impossible [36]. The

deoxygenation and neuropraxia will raise the production of fibrogenic factors in charge for important changes in the erectile tissue, destroying smooth muscle cells, reducing the elasticity of the corpus cavernosum, and finally veno-occlusive dysfunction [37]. In this circumstances, the aim of all treatments are to preserve functional oxygenation of the tissue in the first phase. Montorsi et al., concluded that the early postoperative locally administration of alprostadil enhanced EF recovery rates [38]. Padma-Nathan et al. also published a study in which they gave sildenafil nightly or placebo for 36 weeks to the ORP patients and they concluded that patients recovered EF [39]. The patients obtained after a 8 week drug free period, improvements in nocturnal penile erections and better IIEF scores than the patients treated with placebo.

In conclusion the patients should be counselled postoperatively regarding the optimal rehabilitation treatment to increase the changes of re-gaining erectile function.

2. Penile prostheses

Penile prosthesis implantation is considered another treatment option for patients with ED, after radical prostatectomy [40]. The penile prostheses are recommended only after the failure of the pharmaceutical treatment [40]. The literature studies presented excellent reports about the satisfaction rates of patients and theirs partners [41], but on the other hand penile prostheses are underused in the management of erectile disfunction after RP.

Conclusions

In conclusion we are living in the era of early diagnosis of PCa with outstanding oncological outcomes and new surgical methods, an era where the quality life and erectile function of the patient became very important aspect. In this context the doctors should be aware of applying correct strategies to increase post radical prostatectomy erectile function recovery using comprehensive clinical management and establishing a personalized profile for each patient.

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REVIEW

HPV Infection and Vulvar Cancer

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Abstract

Vulvar cancer is an uncommon gynecological malignancy primarily affecting postmenopausal women and is the fourth most common gynecologic cancer. There is no specific screening and the most effective strategy to reduce vulvar cancer incidence is the opportune treatment of predisposing and preneoplastic lesions associated with its development. Vulvar carcinoma can be HPV-positive or HPV- negative. Any suspicious vulvar lesion should be biopsied to exclude invasion.

Key words: HPV, infection, vulvar cancer.

Introduction

HPV infection plays a central role in the development of vulvar cancer, HPV 16 and 18 are the most frequently reported genotypes that might induce this kind of lesions. It has been demonstrated that HPV infection plays a central role in the development of other malignancies such as vulvar, vaginal or anal cancer in women and anal or penile cancer in men [1]. Squamous cell carcinoma (SCC) of the vulva, the most common subtype, has traditionally been regarded as a disease of postmenopausal women, although the mean age of incidence has fallen in recent years owing to the increase in HPV infections worldwide [2, 3]. Squamous cell carcinomas represent more than 90% of all vulvar cancer and are associated with several histopathological subtypes such as keratinized, basaloid warty or verrucous lesions [4]. The high-risk HPV types 16,

31 and 33 are frequently detected in vulva cancer and its precursor lesions (VIN). Vulva cancer with basaloid histopathology in young women is often associated with HPV-69 [1, 5, 6, 7].

Diagnosis

Any suspicious vulvar lesion should be biopsied to exclude invasion. This can be done under local anesthetic with a 3 or 4 mm Keyes biopsy instrument, or with an incisional or wedge biopsy. Even if the lesion is small, it is better not to excise the entire lesion at the time of biopsy, as this makes the subsequent definitive surgery difficult to plan [8].

Risk factors

Risk factors for vulvar cancer include smoking, vulvar dystrophy, HPV infection, a history of high-grade CIN, VIN, and immunodeficiency syndromes (HIV infection) [9, 10]. The rate of VIN progression to invasive vulvar carcinoma is low [11, 12]. Definitive surgery is the first treatment for early-stage vulvar cancer [13, 14]. The studies indicated that the use of condom and really circumcision reduces the risk of HPV infections, and subsequently CIN and VIN in women andpenile lesions in men [15, 16].

Cigarette smoking was found to increase the risk of CIN3 and cervical cancer among women infected with oncogenic HPVs as compared to women who do not smoke. A synergistic effect was reported between cigarette smoking and HPV16 DNA load for development of cervical cancer in Sweden women [17]. The impact of cigarette smoking has focused on humoral immune responses to HPV and on the prevalence, incidence, and persistence of HPV infections [17]. A recent in vitro study demonstrated that exposure of cervical cells to Benzoapyrene, a major carcinogen in cigarette smoke, stimulates higher levels of virion synthesis in HPV-infected cells. On the other hand, the researchers showed that among smokers, the viral load did not change significantly by the intensity and duration of cigarette smoking, suggesting a low threshold for the effect of smoke on HPV DNA load [17].

Symptoms

While vulvar cancer may be asymptomatic, most women present with vulvar pruritus or pain, or have noticed a lump or ulcer. They may also have abnormal bleeding or discharge, and many will have a history of vulvar symptoms due to underlying lichen sclerosis or HSIL. Advanced vulvar cancer may present with a lump in the groin due to lymph node metastases [8].

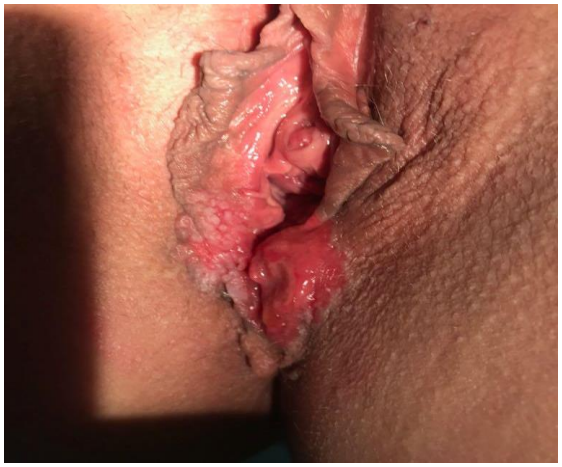

Fig.1: Invasive vulvar squamous cellcarcinoma with HPV 16 infection

(Personal archive Dr. Florica Șandru)

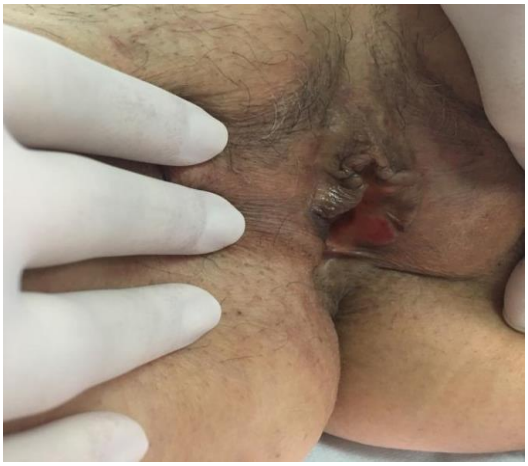

Fig. 2: Vulvar intraepithelial neoplastic lesion stage III

(Personal archive Dr. Florica Şandru)

Investigations

1. Cervical cytology, and colposcopy of the cervix and vagina, if applicable, due to the association of HPV-related cancers with other squamous intraepithelial lesions [18]. Full blood count, HIV testing, biochemical profile, liver profile [18].
2. Chest X-ray [18].
3. CT or MRI scan of the pelvis and groins may be helpful, especially for locally advanced tumors, to detect any enlarged lymph nodes in the groins or pelvis, erosion into underlying bone, or other metastases [19]. In addition, CT or MRI could be useful in further treatment planning.
4. ^{18}F fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET-CT) can more effectively assess and detect inguinofemoral lymph node involvement compared with CT, influencing the planning of primary surgery and inguinal lymph node dissection to determine the optimum surgical extent without sentinel lymph node dissection and use of frozen sections [19]. Additionally, PET-CT might be used with larger tumors when metastatic disease is suspected or in the recurrence scenario [20].

Histopathological types

Squamous cell carcinomas (SCC) account for the vast majority of vulvar cancers (more than 80%), and melanomas are the next most common cancer. Rarer histological types include:

1.Basal cell carcinoma
2. Verrucouscarcinoma
3. Paget's disease of the vulva
4. Adenocarcinoma,not otherwise specified
5. Bartholin gland carcinoma [18]

Histological grades

1. GX: Grade cannot be assessed
2. G1:Well differentiated
3. G2:Moderately differentiated
4. G3:Poorly or undifferentiated [18]

Treatment

The treatment of vulvar cancer depends primarily on histology and staging. Other variables influencing management are age, coexistence of comorbidities, and performance status of the patient. Treatment is predominantly surgical, particularly for SCC, although concurrent chemo-radiation is an effective alternative, particularly for advanced tumors, and those where exenteration would be necessary to achieve adequate surgical margins [21]. Management should be individualized, and carried out by a multidisciplinary team in a cancer center experienced in the treatment of these tumors [22,23]. Other therapies such as chemotherapy and immunotherapies are usually reserved for metastatic or palliative settings, or for the treatment of rare diseases such as melanoma [23-26].

Conclusions

HPV infection has a central role in developing premalignant or malignant vulvar lesions. Patients diagnosed with HPV-related lesions tend to have a younger age at diagnosis, especially due to the

association with the presence of this virus. When it comes to the prevention of these lesions, it seems that anti-HPV vaccination might play a role.

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REVIEW

The Influence of Anxiety and Depressive Syndrome on Treatment Adherence in Diabetes Mellitus

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Abstract
Diabetes mellitus (DM) is the chronic disease with the prevalence in a continuous rise – reaching a percent of 8.5% from the general population in 2014. Depression is a medical condition more frequently associated with chronic illness such as DM and highly associated with a more reduced quality of life and adherence to medical recommendations. We used the PubMed library and searched after the following key-words: type 1 diabetes mellitus, type 2 diabetes mellitus, anxiety, depression, depressive syndrome, treatment adherence, life quality. Diagnose of a new condition such as DM may be a traumatic experience for patients which could deny the reality, could accuse others of their problems or could refuse to go for a second opinion medical advice, to admit the truth. The newly diagnosed cases of type 2 DM benefit from unique medical training just from the perception of the illness point of view, while the evolution of parameters such as HbA1c does not differ significantly compared with usual care. Also, in newly diagnosed patients with type 2 DM, there is a higher incidence of depression and lower mental quality of life.

Key words: diabetes mellitus, quality of life, depression, newly diagnosed diabetes mellitus, treatment adherence.

Introduction.

Diabetes mellitus (DM) is the chronic disease with the prevalence in a continuous rise – reaching a percent of 8.5% from the general population in 2014 [1]. There are two main types of diabetes known – type I or autoimmune diabetes, secondary to β pancreatic cells deficiency developed through auto-antibodies; and type II, developed by insulin resistance, fact that progressively exhaust the pancreatic secretion of insulin [2].

Diagnose of a new condition such as DM may be a traumatic experience for patients which could deny the reality, could accuse others of their problems or could refuse to go for a second opinion medical advice, to admit the truth. On the other hand, there are the patients that had a long evolution from the moment of diagnosing of their condition. These two categories of diabetic patients have different influences from the depressive syndrome – the first category tends to be more willing to do something in order to influence the disease evolution, while the second one tends to be more at

peace saying that this is the natural course of life, respectively ageing, and that earlier or later they would inevitably have to face the reality [3, 4].

The most sensible category of patients is represented by the one that develops a chronic disease over an already established depressive syndrome. This type of patients will benefit fully from the intervention of professional therapy.

An essential element to take into consideration for patients with the depressive syndrome is the socio-economic status because it profoundly influences the adherence to treatment by exaggerating the perception of how unfavourable things are.

Two important concepts mentioned in several studies refer to the anthropological framework of syndemics and chronicity, with the accent on the first of them. Syndemics refers to the holistic view of the patient – not only the individual experience reflected in the epidemiological context is important, but, also, the socio-cultural environment of the patient, the political decisions that affect the patient's situation. So, the authors emphasise on taking more into consideration aspects like poverty, stress encountered by a population or social relationships that could affect the well-being of patients. Chronicity describes the alteration that a chronic disease produce in a patient, how this never-ending process influence patients life, choice in being adherent to a treatment or to a recommendation of follow-up that are so important in such ailments and how the impact of its financial status or the context of its country (e.g. war, economic crisis) determines or forces him to neglect its health.

Material and Methods

We used the PubMed library and searched after the following key-words: type 1 diabetes mellitus, type 2 diabetes mellitus, anxiety, depression, depressive syndrome, treatment adherence, life quality. We select the article who were directly linked with our purpose. After we analysed the library, we included 11 studies referring to the connection between DM and depression in either direction.

Results and Discussions

Interpretations from studies of Poverty, Depression, and Diabetes presents this concept by two case studies. Firstly, they present the case of a Mexican female, with chronic ailments - DM and depression, uneducated – because as a young person she had to take care of her siblings, who lived in poverty - she married with a diabetic alcoholic husband who neglected his ailment until he hanged himself, who refuges with her daughter in Chicago – where she works under-the-counter and has to face the same story – her daughter is abused, so she takes her grandson and move separately, but, because she has to take care of him, she neglects her diseases; fact that emphasizes the VIDDA syndemic. The second case, a female orphan who marries and have kids, but because they have no extended family in Delhi are trapped to work a low paid job which provides them with a room, so she became underweight and depressive, neglect her health because of poverty and finally associate DM, being trapped in the vicious circle of not being able to take a better-paid job, feeling bad because of the neglected diabetes symptoms and feeling incapable of building a future for her children [5].

In ”Beyond Comorbidity: A Critical Perspective of Syndemic Depression and Diabetesin Cross-cultural Contexts” article, they discuss several topics such as that the comorbidity from the anthropological point of view refers to somatisation or to the way social environment influence comorbidities, not interwining their intervention or that syndemics is the key concept that takes into consideration not only the relationship between environment and ailments but, also, with disease distribution across a certain

population. Also, they try to answer the question if syndemics is a transnational problem and they answer with a certain yes, on the consideration of the diversity met across geographical, cultural and economic coordinates. They, also made a 60 people narrative interview study in Urban India, that emphasize that the incidence of DM, depressive symptoms increase with the lowering of social status. In South Africa, they conducted the historical interview study only on 27 available females stated that DM prevalence starts to increase from the middle-class and is highly influenced by the food insecurity or unsafe of their neighbourhood [6].

A cross-sectional survey in Brasil, with three-stage randomization with 60202 individuals included analysed two patients presenting DM or depressive symptoms. The results included the fact that only 0.91% patients presented both DM and depressive symptoms, the clustering of these two ailments is favourited in obese patients and females with short education and low income – condition frequently found in the case of females that suffered from violence. Another important conclusion is that the association between DM and depression lead to higher rates of disability. Taking into consideration the context that Brazil is a large country with a high variability of its inhabitants, there is hard to draw some firm conclusions, because of the economic and educational factors that are highly influencing the problem and which are unevenly distributed [7].

”Depression in diabetes mellitus: a comprehensive review”, states that depression despite its high prevalence, associates a high recurrence and persistence, decreasing the quality of the patients` life making it a significant determinant of the patients` compliance and, especially, adherence to the medical recommendations. Also, depression proved in a 4385 diabetic patients study to be severely underdiagnosed (49%) and only almost a third (31%) of the patients received correct dosage or amount of the medication and psychotherapy. There is also recommended a multidisciplinary approach in diabetic patients that associated depression [8].

In the other important study regarding the link between depression and diabetes, they aimed to evaluate the diabetic patients through the prevalence of anxiety and depression using the Beck inventory questionnaires for this two pathologies and taking into consideration demographic elements such as age, gender, level of education and occupational status. The study results are that from the total of 184 diabetic patients, depression was found in 70.7% of cases, while anxiety was identified in 69.6% of cases. Moreover, the relation between diabetes and depression was discovered to be affected by sex (OR: 2.767), age (OR: 2.222), level of education (OR: 4.145) and job status (OR: 3.901), while the relation between diabetes and anxiety is influenced by gender (OR: 2.274), age (OR: 2.706) and Job Status (OR: 2.441). The conclusions drawn were that DM associates highly with depression and anxiety and that these interactions are amplified by factors related to the socio-economic status of the patient: age, gender, job and education [9].

”Depression and diabetes – Impact of Depressive Symptoms on Adherence, Function and Costs" evaluated the symptoms of depression and their influence on the adherence to medical recommendations and costs derived from it in a primary care setting for DM. They included 367 patients with both type 1 and 2 of DM from two different centres who received questionnaires to provide the necessary data. After distributing the patients in tertiles after the depressive symptoms severity, they obtained that adherence decreased from the medium tertile. The biggest difference regarding the days in non-adherence to oral

hypoglycaemic regime proved to be between the high and low tertiles, almost two-fold higher (7% vs 15%). Other relevant differences encountered were higher costs for the healthcare system, because of a higher probability to need medical assistance or inpatient, poorer outcomes and poorer physical and mental function [4].

The review ”The association between Diabetes mellitus and Depression” aimed to emphasize the link between DM and depression and to understand its physiopathology mechanism. What is important to say is that even the World Health Organization warns us about the serious gap that is between mental health problems and the resources that are used to treat them. However, what is most important is that the diabetic specialist to pay attention to this frequent comorbidity associated with DM and to manage it a multidisciplinary team, to minimize the patient's number of DALYs or, even, to decrease the mortality [10].

”Depression and Quality of Life in Patients with Diabetes: A Systematic Review from the European Depression in Diabetes (EDID) Research Consortium" included 20 studies (18 cross-sectional and two longitudinal) related to diabetic patients regarding their quality of life, even if they associate or not depressive symptoms. The results found a moderate negative association between depressive symptoms and generic quality of life in diabetic patients, especially regarding the physical and mental health, a moderate to severely negative association between depressive symptoms and specific quality of life in diabetic patients regarding their satisfaction with the treatment or with the idea of the treatment that they have to adhere to, a mild to moderate positive association between depressive symptoms with domain-specific quality of life with a greater reporting for functional limitations, a lower self-reported health and cognitive impairment [11].

In ”Effectiveness of a diabetes education and self-management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three-year follow-up of a cluster randomised controlled trial in primary care”, a multicentre randomised controlled trial in primary care with 824 patients newly diagnosed with type 2 DM from 207 centres, a six hours educational programme was compared with usual care by glycated haemoglobin (HbA1c) level and by secondary outcomes like smoking status blood pressure, depression and emotional impact of diabetes. The included patients were divided into a control group of 387 patients and an intervention group of 437 patients, with a total of 743 patients that were eligible at the three-year follow-up. The results state that there were no significant differences in case of a single educational programme for newly diagnosed type 2 DM patients, but the benefits were gained in several illness beliefs, such as a decrease in the proportion of non-smokers at 12 months, but it ceased at three years follow-up or in a better understanding of the disease with a better ability to cope with it [12].

”Increased Depression Symptom Score in newly diagnosed Type 2 Diabetes Patients” analysed the data from DIAREG registry – 1807 type 2 DM patients from which only 270 cases had completed all outcome questionnaires. Approximatively half of the patients have a long duration of DM evolution, but with a well-controlled disease. What is important to emphasize is that the patients with short DM evolution – shorter than two years, presented higher depressions scores and a lower average mental sum score [13].

Analysing the depression even more, in the article ”Investigating Factors Associated with Depressive Symptoms of chronic Kidney Diseases in China with Type 2 Diabetes” has evaluated the depression in patients with type 2 DM and chronic kidney

disease (CKD), by a cross-sectional analytic study that included 210 patients with both type 2 DM and CKD. This study confirmed that the quality of life is inversely correlated with depression. Also, depression was found in 21.4% of diabetic patients and was proved to be statistically significantly associated with female gender, yearly income, clinic visit frequency, blood glucose monitoring frequencyand duration of diabetes, while the depressive symptoms had higher rates in IV-V stage of CKD comparatively with I-III stages and using stepwise logistic regression they found out that in a patient with type 2 DM and CKD a predictor for developing depressive symptoms are represented by female gender, complicated arterial hypertension and the severity of type 2 DM related to CKD [14].

Conclusions

Chronicity is an important element that states that socio-economical, demographical factors influence not only chronic illnesses but, also, that chronic illness influences each other evolution, progression and instalment. Syndemics points out that certain factors (sociological, demographical, geo-political) influence an ailment, but, also, the cultural, environmental or economic factors are involved. An excellent example is that Brazilian epidemiological analysis that shows that even if there are found out some facts that seem to allow drawing a firm conclusion, they are highly influenced by the uneven distribution of the inhabitants – from the economic and cultural point of view, especially in a large country, in short by syndemics.

DM not only that is highly associated with depression, but their mix and a low rate of correctly diagnosing and adequate treatment result in its persistence and recurrence, amplifying the impact of the already existing comorbidities. So, there is very important that the diabetic specialists take it seriously into consideration and so to prevent the increased number of patients DALYs or, even, the patient's mortality. DM is highly associated with depression and anxiety, and these associations are influenced by factors like age, education, job or gender. Moreover, higher severity of the depressive symptoms transcripts in a higher burden for the healthcare system through the higher need for medical assistance – ambulatory or as an inpatient, lower prognosis, outcome or physical function.

Quality of life - with its components generic and domain-specific, declines in the presence of depressive symptoms. Moreover, the person with diabetes that associates depressive symptoms have a lower specific quality of life, thus, supposing to be a good predictor for developing functional limitation in the future.

The newly diagnosed cases of type 2 DM benefit from unique medical training just from the perception of the illness point of view, while the evolution of parameters such as HbA1c does not differ significantly compared with usual care. Also, in newly diagnosed patients with type 2 DM, there is a higher incidence of depression and lower mental quality of life.

In patients with type 2 DM with CKD, depression is predicted to appear by factors like female gender, complicated arterial hypertension and the severity of type 2 DM related to CKD.

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