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Editorial

The most important gynaecological event is going to be celebrated: the 2012 FIGO World Congress will be held in Rome next October. The Italian Journal of Gynaecology and Obstetrics participate in this event modyifing the language of its articles from Italian to English in order to be more easily read by our foreign colleagues. We want to offer the best of the Italian research and I am sure we have a lot to share with everybody who is interested in this important field of medical science.

The editorial staff of the Italian Journal hopes that italian researchers will participate in the top of the Congresses with the best of their knowledge. Grants in medical research have never been distributed to a great extent but they have been cut off in this period of financial crisis, when the funds available have been redirected towards other social needs.

Research, anyway, cannot be stopped or delayed particularly in the medical field. Health must be considered the most important goal to achieve by medical doctors and we want the best for our women.

Pull yourself together in research and communication! The Italian Journal is ready to spread your results to the whole obstetrical and gynaecological community.

Articles published in this issue range from obstetrics to family planning, from minimal surgery to IVF giving a large overview of Italian research in obstetrics and gynaecology… and we want to do better and better.

Nicola Natale

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Psychometric tests and risk factors for screening of mood disorders in pregnancy and post-partum: a preliminary study

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ABSTRACT

Psychometric tests and risk factors for screening of mood disorders in pregnancy and post-partum: a preliminary study.

Pregnancy and childbirth are events of intense biological work as an hard psychological mobilization. Anxiety and sadness reactions are common in these periods, so that some patients develop mood disorders, such as postpartum depression, bipolar disorder, puerperal psychosis. Aim of this study is to determine sensitive and specific psychometric tests and risk factors for the prevention of these conditions. A group of patients was recruited during pregnancy (149 patients), at 2-3 days (69 patients) and 4-6 weeks after birth (12 patients at present), submitting two psychometric tests (EPDS and HCL-32) and a questionnaire for the analysis of risk factors. In pregnancy, 14.1% of the sample were positive at EPDS test and 39.6% at HCL-32. 2-3 days after birth: 17.4% of patients were positive at EPDS test and 43.5% at HCL-32. At 4-6 weeks postpartum evaluation: 33.3% of the sample were positive at EPDS test, 16.7% at HCL-32. Risk factors significantly associated with positivity for postpartum EPDS resulted: "previous induced abortion" (p=0.004), "previous miscarriages" (p=0.028), "previous psychiatric treatment" (p=0.028) "positive EPDS test before birth "(p=0.006). "Being in Italy for less than 6 months" is associated with both positive tests EPDS (p raw = 0.001) and HCL-32 (p=0.032).

These preliminary results show that psychometric tests should be used not only in post-partum, but also in pregnancy as an instrument of prevention of mood disorders and post-partum depression in the presence of significant risk factors. Further consideration will need a sample of more patients.

Key words: pregnancy, post-partum depression, bipolar disorders, EPDS, HCL-32.

SOMMARIO

Test psicometrici e fattori di rischio per lo screening dei disturbi dell'umore in gravidanza e post-partum: uno studio pilota.

La gravidanza e il parto sono eventi di intenso lavoro biologico e di complessa mobilitazione psicologica, a tal punto che alcune pazienti sviluppano veri e propri disturbi dell'umore. Scopo dello studio è quello di individuare fattori di rischio e test psicometrici, sempre più sensibili e specifici, per la prevenzione e la diagnosi precoce di queste problematiche. È stato reclutato un campione di pazienti in gravidanza (149 pazienti), rivalutato 2-3 giorni dopo il parto (69 pazienti) ed a 4-6 settimane dal parto (al momento 12 pazienti), proponendo due test psicometrici (EPDS ed HCL-32) ed un questionario per l'analisi dei fattori di rischio. In gravidanza il 14,1% del campione risultava positivo ad EPDS; il 39,6% ad HCL-32. 2-3 giorni dopo il parto: il 17,4% delle pazienti risultava positivo ad EPDS e il 43,5% ad HCL-32. A 4-6 settimane dal parto: il 33,3% del campione risultava positivo ad EPDS, il 16,7% ad HCL-32. I fattori di rischio significativamente associati a positività ad EPDS dopo il parto risultavano: "pregressa interruzione volontaria di gravidanza"(p=0,004), "pregressi aborti spontanei"(p=0,028), "precedenti trattamenti psichiatrici" (p=0,028) "positività al test EPDS prima del parto" (p=0,006). "Essere in Italia da meno di 6 mesi" è associato a positività ad entrambi i test EPDS (p grezza = 0,001) e HCL-32 (p=0,032). I risultati, del tutto preliminari, indicano come i test psicometrici debbano essere utilizzati non solo nel post-partum ma anche in gravidanza come strumento di prevenzione dei disturbi dell'umore e/o depressione nel post-partum in presenza di fattori di rischio significativi. Ulteriori valutazioni sono necessarie su un campione più elevato di pazienti.

Parole chiave: gravidanza, depressione post-partum, disturbo bipolare, EPDS, HCL-32.

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INTRODUCTION

Pregnancy and childbirth are complex events, packed with physical and psychological incidents as well as a profound biological, social and emotional transition (1). Although reactions of anxiety and sadness are common during pregnancy, most women go through this period of their life without major psychopathology. "Maternity blues"(2) is a benign psychological alteration occurring in the first days after delivery in 30-80% of women. Characteristic symptoms are crying, confusion, anxiety, mood lability, insomnia, low self-esteem, guilt, eating disturbances and dysphoria. Symptoms typically last from a few hours to several days and peak on 4th-5th day after delivery, have few negative sequelae and do not require treatment. However, sometimes these symptoms persist and degenerate into a real major depressive disorder. Depression is the leading cause of "burden of disease" in women between 15 and 44 years and the second leading cause in women between 45 and 59 years (3). Therefore, these disorders concern patients in fertile age who have to face them during pregnancy and puerperium. In general the term "postpartum depression" is often used to characterize any depressive symptoms occurred after the childbirth. Actually, in literature, *postpartum depression* refers to a non-psychotic depressive episode that begins in or extends into the postpartum period, that lasts more than 2 weeks, and that meets criteria for a major depression. Marcé Society, an international organization for the study of psychiatric illness related to childbearing, recognizes the time of vulnerability for postpartum depression as one year after delivery (4). Previous data show a prevalence of depressive symptoms between 8% and 51% and a prevalence of Major Depressive Disorder between 10% and 17%. Its symptoms include: sadness, hopelessness, low self-esteem, guilt, sleep and eating disturbances, exhaustion, emptiness, anhedonia, social withdrawal, feeling inadequate in taking care of the baby, increased anxiety or panic attack.

The etiology of postpartum depression is not well known. Three major pathophysiological hypothesis have been considered:

- changes in woman's hormones during pregnancy: the prolonged hypogonadic state can determine serotoninergic activity reduction and the consequent depressive symptomatology development;
- psychosocial factors: personal history, psychoaffective life, problematic pregnancy, lifestyle changes, pre-existing mental illnesses, stressful circumstances, problematic delivery (5,6);
- biochemical changes: according to the inflammatory and neurodegenerative hypothesis, pro-inflammatory cytokines increase can determine the growth of the cerebral oxidative stress, variation in the hypothalamic-pituitary-adrenal axis, the excessive toxic catabolites of tryptophan production that induce neurodegeneration, and the reduction of neurotrophines (7).

Postpartum depression affects women mental health and compromise emotional and cognitive development of the newborn.

Postpartum psychosis is a severe and rare disorder affecting 0.1-0.2% of mothers (2). Most postpartum psychoses begin within 3th weeks after delivery. Symptoms include thought disturbances, delusions, hallucinations, disorganized speech or behavior and gross impairment in functioning. Affective symptoms are most prominent. Approximately 70-80% of postpartum psychoses affects women prone to bipolar disorder. Recent studies suggest that most of patients at first diagnosed as suffering from post-partum depression, after are recognized as bipolar patients. Bipolar disorder (8) is a mood affection characterized by the alternative periods of mood expansion (mania) and deflection (depression).

In retrospective and prospective studies, approximately 60-70% of women affected by bipolar disorder experienced a mood episode during pregnancy and the postpartum period (9). Women with bipolar disorder are over 23 times more likely to be admitted to the hospital because of a mood disorder within 30th days after delivery compared to during the pregnancy. Women affected by bipolar disorder seems to be at high risk to develop a post-

partum depressive episode. Moreover, estimates suggest that between 25% and 50% of women affected by bipolar disorder experience postpartum mania and psychosis (10).

Recently, the attention on the problem of unipolar depression during pregnancy and postpartum has been increased; however not enough has been done in the clinical practice in order to identify patients at risk during routine checkup. Furthermore, common screening methods for post-natal depression does not allow accurate diagnoses for bipolar disorder, and therefore can't detect patients at risk for depression or puerperal psychosis.

OBJECTIVES

Considering an early screening in order to find risk factors, our aim is to develop strategies of prevention and treatment of mood disorders in women during pregnancy and postpartum.

Our study had three main focuses:

- to deepen the knowledge about postpartum depression, obtaining data related to the mood in women during late pregnancy and the postpartum period;
- to find a correlation between risk factors and the development of mood disorders during pregnancy and post-delivery;
- to elaborate a set of psychometric tests in order to predict mood alterations in pregnant both in case of a deflection and in case of an expansion of the tone.

MATERIALS AND METHODS

A population of mothers recruited from the outpatient clinics of our hospital Policlinico "A. Gemelli", Catholic University of Sacred Heart in Rome, has been analyzed. An anamnestic questionnaire (Figure 1), related to anagraphic, clinical and socio-cultural information was proposed, in order to identify risk factors.

As reported in literature, risk factors detection is provided with low sensitivity and specificity in women at risk for mood disorders. Therefore, to improve sensitivity and specificity, patients were asked to fill out the Edinburgh Postnatal Depression Scale (EPDS) and the Hypomania Checklist Symptoms (HCL-32). Data on the type of delivery, use of epidural analgesia and the duration of labor were also recorded. Besides, patients were evaluated by a psychiatrist through a full clinical interview.

The Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS) is a 10-item self-report scale, specifically designed to screen for postnatal depression in community samples (11). Each item is scored on a 4 point scale (0 to 3), the minimum and maximum total score ranging from 0 to 30 respectively.

The EPDS is easy to administer and has proven to be an effective screening tool. Mothers who score above 10 are likely to be suffering from a varying severe depressive illness. The EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates the mother's felling during the previous week. In doubtful cases the tool may be repeated after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias or personality disorders.

Hypomania Check List-32

The HCL-32 is a self-rating questionnaire for lifetime history of hypomanic symptoms (12). In clinical practice, many patients firstly diagnosed as unipolar depressives may have an unrecognized bipolar disorder. Identifying these "hidden" bipolar cases is important in order to ensure proper, effective treatment.

HCL-32 can be used for screening bipolar-II, minor BP and subthreshold hypomania. The HCL-32 does not provide a diagnosis of bipolar disorder, but can aid potential bipolar cases in psychiatric, psychological and general practice.

The total score is the number of positive answers to the 32 items listed in question 3. Individuals with a total score equal to or over 14 are potentially bipolar and should be carefully interviewed about their previous own and family history.

A positive HCL-32 gives further information about hypomanic disorder or mixed status typical features, with no interference with a diagnosis of postpartum depression.

Anamnestic Questionnaire	Yes	No
1. Is this your first pregnancy?		
2. Did you have any problems to get pregnant?		
3. Is this a unexpected pregnancy?		
4. Did you were in doubt to terminate the pregnancy?		
5. Was the current pregnancy obtained by artificial insemination?		
6. In the past have you ever performed artificial insemination?		
7. In the past have you ever performed voluntary abortion?		
8. Did you ever had miscarriages?		
9. Is this pregnancy difficult?		
10. Have you suffered from vomiting during pregnancy, after the third month?		
11. Are you suffering from gestational hypertension, gestational diabetes or other pathologies?		
12. Are you married?		
13. Do you cohabit with your partner?		
14. Did you cohabit with other partners in the past?		
15. Have you had any other children by other partners?		
16. Have you a problematic relationship with your partner?		
17. Do you have an unstable job that does not protect pregnant women?		
18. Have you had any recent job discomforts (loss or change of employment, mobbing, problems with colleagues / employer)?		
19. Can you rely on help and support of your partner?		
20. Can you rely on help and support of your family?		
21. Can you rely on help and support of your partner's family?		
22. Can you rely on help and support of your friends?		
23. Did you recently change neighborhood or city?		
24. Have you had serious economic problems?		
25. In the last year have you suffered a close bereavement?		
26. Does your culture or religion make you feel emarginated?		
27. Do you live in Italy since less than 6 month?		
28. During pregnancy did you suffer from anxiety, panic or depression?		
29. Have you ever consulted a psychologist for a visit?		
30. Have you ever consulted a psychiatry for a visit?		
31. Have you ever made psychotherapy?		
32. Have you ever used "psychiatric" drugs (anxiolytic, antidepressants, antipsychotics, other)?		

Figure 1. Anamnestic questionnaire.

Patients were evaluated in three times:

- third trimester of pregnancy (T0): 35-37 weeks of pregnancy;
- 2-3 days postpartum (T1);
- 4-6 weeks postpartum (T2).

In order to evaluate groups differences, logistic regression and Chi-squared tests for quantitative and qualitative variables respectively were used. Age and all variables with a *p*-value lower than 0.25 were introduced in the logistic regression model, as suggested by Hosmer and Lemeshow (13). Variance inflation factor (VIF) was used to test for collinearity. The best models were chosen with the backward: Wald method. The analysis was performed using SPSS software version 12.0 for Windows and statistical significance level was set at p=0.05.

RESULTS

We studied 149 patients from 19 to 44 years of age. Median age of the patients was 34 years. All patients could speak Italian and understand tests we asked to fill out.

21 patients were positive at EPDS test (14.1% of the sample) and 59 (39.6%) were positive at HCL-32 before delivery. 12 patients (8.1%) were positive for both tests before delivery.

80 patients were lost at follow up (53.7% of the whole sample). There were no statistically significant differences in positivity at EPDS and HCL32 tests among populations which were lost at follow up.

Following data are related to the 69 patients who were still in the study after delivery: 12 (17.4%) were positive at EPDS test and 30 (43.5%) were positive at HCL-32 test. 7 of 69 patients (10.1%) were positive at both tests after delivery.

The evolution of positive patients at the time T0 and T1 is summarized in Tables 1 and 2.

At the third time of evaluation (4-6 weeks postpartum) there are at present only 12 patients: 4 patients (33.3%) were positive at EPDS test and 2 patients (16.7%) were positive at HCL-32 test. No patient (0%) were positive for both tests. Evaluation on the rest of the sample is still in progress.

Risk factors analysis takes count of the age and all the answers to the anamnestic questionnaire. Only factors showing a p <0.250 by univariate analysis were included in the logistic regression model.

Table 1 - Clinical evolution of patients with positive EPDS at T0→ T1.

EPDS	
T0	**T1**
	12 patients lost (57.1%)
21/149 positive (14.1%)	5 patients are still positive at T1 (23.1%)
	4 patients become negative at T1 (19%)

Table 2 - Clinical evolution of patients with positive HCL-32 at T0→ T1.

HCL-32	
T0	**T1**
	37 patients lost (62.72%)
59/149 positive (39.6%)	13 patients are still positive at T1 (22.03%)
	9 patients become negative at T1 (15.25%)

Results of the univariate analysis are summarized in Tables 3 and 4. "Previous voluntary interruption of pregnancy" (crude p=0.004; crude OR: 7.35; 95%CI: 4.00 – 13.51), "previous miscarriage" (crude p=0.028; crude OR: 0.76; 95%CI: 0.65 – 0.89), "previous psychiatric treatment" (crude p=0.028; crude OR: 6.71; 95%CI: 3.79 – 11.90) and "EPDS positivity before delivery" (crude p=0.006; crude OR: 9.46; 95%CI: 2.04 – 43.84) were all associated to EPDS test positivity after delivery, but significance was lost at the multivariate analysis. "Being in Italy for less than 6 months" was associated to positivity to both EPDS (crude p=0.001; crude OR: 10.00; 95%CI: 2.48 – 40.30) and HCL32 (crude p= 0.032; crude OR: 4.38; 95%CI 1.21 – 15.78) and significance persisted in the regression models.

Multivariate analysis results are summarized in Table 5: the best predictive model for EPDS test positivity after delivery included marital status (being married is a protective factor: adjusted OR: 0.13; 95%CI: 0.02 – 0.83) and "Being in Italy for less than 6 months" (adj. OR: 6.92; 95%CI: 1.10 – 43.48); the best predictive model for being positive at HCL32 test after delivery included age as a protective factor (adj. OR: 0.84; 95%CI: 0.74 – 0.97) and " Being in Italy for less than 6 months" (adj. OR: 4.64; 95%CI: 1.09 – 19.62).

Table 3 - Results of the univariate analysis (risk factors for EPDS positivity).

	EPDS –positive among unexposed	EPDS –positive among exposed	crude p
Voluntary interruption of pregnancy	11/68 (16.2%)	1/1 (100%)	0.174
Previous miscarriages	12/50 (24.0%)	0/19 (0%)	0.028
Disorders of pregnancy	9/60 (15.0%)	3/9 (33.3%)	0.183
Married	5/17 (29.4%)	7/52 (13.5%)	0.152
Previous marriage or cohabitation	9/60 (15.0%)	3/9 (33.3%)	0.183
Hardships at work	8/59 (13.6%)	4/10 (40.0%)	0.064
Social exclusion for religious reasons	11/68 (16.2%)	1/1 (100%)	0.174
In Italy for less than six months	5/55 (9.1%)	7/14 (50.0%)	0.001
Previous psychiatric treatment	10/67 (14.9%)	2/2 (100%)	0.028
Previous psychotherapy	8/59 (13.6%)	4/10 (40.0%)	0.064
Previous psychiatric pharmacotherapy	8/61 (13.1%)	4/8 (50.0%)	0.026
Analgesia at delivery	4/10 (40.0%)	6/52 (11.5%)	0.046
EPDS –positive before delivery	7/60 (11.7%)	5/9 (55.6%)	0.006
Age			0.991*

* logistic regression.

Table 4 - Results of the univariate analysis (risk factors for HCL-32 positivity).

	HCL32 –positive among unexposed	HCL32 –positive among exposed	crude p
Disorders of pregnancy	24/60 (40.0%)	6/9 (66.7%)	0.163
Precarious employment	23/58 (39.7%)	7/11 (63.6%)	0.190
Support of partner	2/2 (100%)	28/67 (41.8%)	0.185
Being in Italy for less than six months	20/55 (36.4%)	10/14 (71.4%)	0.032
Previous psychiatric treatment	28/67 (41.8%)	2/2 (100%)	0.185
Pathological course of pregnancy	27/57 (42.1%)	0/4 (0%)	0.147
Analgesia at delivery	1/10 (10.0%)	23/52 (44.2%)	0.073
HCL32 –positive before delivery	16/46 (34.8%)	13/22 (59.1%)	0.071
Age			0.016*

* logistic regression.

Table 5 - Results of the multivariate analysis. Logistic regression models for positivity to EPDS and HCL32 tests after delivery.

Positivity to EPDS after delivery		
Risk factor	**Adjusted p**	**OR (95%CI)**
Married	0.031	0.13 (0.02 – 0.83)
In Italy for less than six months	0.039	6.92 (1.10 – 43.48)
Positivity to HCL32 after delivery		
Risk factor	**Adjusted p**	**OR (95%CI)**
Age	0.015	0.84 (0.74 – 0.97)
In Italy for less than six months	0.037	4.64 (1.09 – 19.62)

DISCUSSION

Our data confirm previous evidences about Postpartum Depression incidence (2) and risk factors contribution in its pathogenesis.

Although we can't assert definitive conclusions concerning the high number of patients positive to HCL-32, this result may be interpreted as consequence of a mood expansion, related to an adaptive reaction of the organism to the stressful period of pregnancy.

At 4-6 weeks postpartum (third time control) patients sample is too small to take conclusions about the incidence of depressive and hyperthymic simptoms (tendency to develop bipolar disorder) and risk factors analysis in mothers population. These statistical evaluations will be conducted as soon achieved a significant sample size.

The results of our study suggests that some psychosocial risk factors are significantly correlated to the presence of depressive symptoms. In particular a women with previous voluntary interruption of pregnancy (crude p 0.004) have a most important positivity to EPDS test, condition already detected in other studies in literature (14,15). Probably the previous induced abortion can determine guilty feelings during the current pregnancy, thoughts and fantasies about the dead baby on the new one, that generate an anxious state, mainly an anticipatory anxiety, and mood changes during pregnancy; previous miscarriages (crude p 0.028) generates in the pregnant anxiety and phobias, due to the fear of reliving the previous trauma. Past history of psychiatric illnesses, in particular previous psychiatric treatment (crude p 0.028), previous psychiatric pharmacotherapy (0.026), previous psychotherapy (crude p 0.064) are anamnestic factors that can predict a future pathologic symptomatology. Moreover, psychiatric pharmacotherapies and treatments are not only statistically significant variables, but reveal the major relevance of the previous psychiatric/psychological patient's problem. Unsolved psychological problems leave patients vulnerable to distresses and can determine mood changes during the special period of pregnancy. Furthermore, none of the patients we evaluated had a psychological or psychiatric therapy during pregnancy. This finding highlights a precarious psychological assistance even in women who had previously shown a tendency to develop anxiety, depression or panic attacks. "Being in Italy from less than 6 months" (crude p 0.001) with "hardships at work" (crude p 0.064) and "social exclusion for religious reasons" (crude p 0.174) show how a lack of the social-affective support can expose to mood changes almost oriented to a mood deflection.

A special consideration is requested for a risk factor that is related to positivity to both scales, HCL32 and EPDS: "Being in Italy from less than 6 months". This factor has proved to be extremely significant both in multivariate and univariate statistical analysis. This high significance cannot be an accident and neither linked to problems in understanding the test,

since all patients enrolled spoke Italian. Even though there are only few studies in literature (16) that analyze the problem of postpartum depression in immigrant women, it has been described how personal and healthcare professionals support can make a significant contribution to the beginning and the evolution of symptoms of postpartum depression (17). The lack of the original family, the sense of social isolation, the feeling of being alone can contribute also to a mood deflection. Immigrants face unique and multiple layers of challenges that may compromise their mental health and prevent them from receiving adequate and equitable care. For immigrant women, many of these stressors are especially compounded in the vulnerable postpartum period, resulting in postpartum depression (17). This result should lead us to plan more carefully the approach of care to these patients, considered the obvious risk of mood disorders.

Analyzing the clinical evolution of the sample, patients with positive EPDS test during pregnancy are at major risk of developing depressive symptoms immediately after birth (crude p 0006): this finding demonstrates the ability of EPDS tests in pregnancy to predict depressive symptoms in post-partum.

About the analysis of labor-delivery data, analgesia at delivery seem to be a protective factor for depression (crude p 0.046): it can be supposed that the use of epidural analgesia allows a less traumatic labor and consequently lead to less stress in the mother in the immediate postpartum (can be supposed that a traumatic experience of the delivery could be lived with particular distress in the immediate postpartum).

An important limitation of our study was the evident patients drop-outs particularly in puerperium. We highlight a poor compliance of patients, often reluctant to perform psychometric tests and to investigate the possible presence of anxiety and mood disorders, especially in the late post-partum.

CONCLUSIONS

Our study confirms that mood disorders are common conditions during pregnancy and puerperium. HCL-32 and EPDS permit to evaluate the entire spectrum of mood symptoms (from hypothymic to hyperthymic dimensions): this new approach may be crucial to identify patients with a mood expansion during pregnancy as part of a bipolar disorder. Also a careful anamnestic examination is necessary to find psychosocial factors related to an increased risk of mood disorders in pregnancy and postpartum. These preliminary results show that psychometric tests should be used not only in post-partum, but also in pregnancy as an instrument of prevention.

As the high prevalence of these disorders, the development of an integrated system of services will likely be important to ensure a systematic screening to pregnant women.

Further researches are needed in order to identify most specific and sensitive psychometric tests for different populations of perinatal women and in order to establish the best practice to prevent and detect early diagnoses of mood disorders in pregnant women and post-partum.

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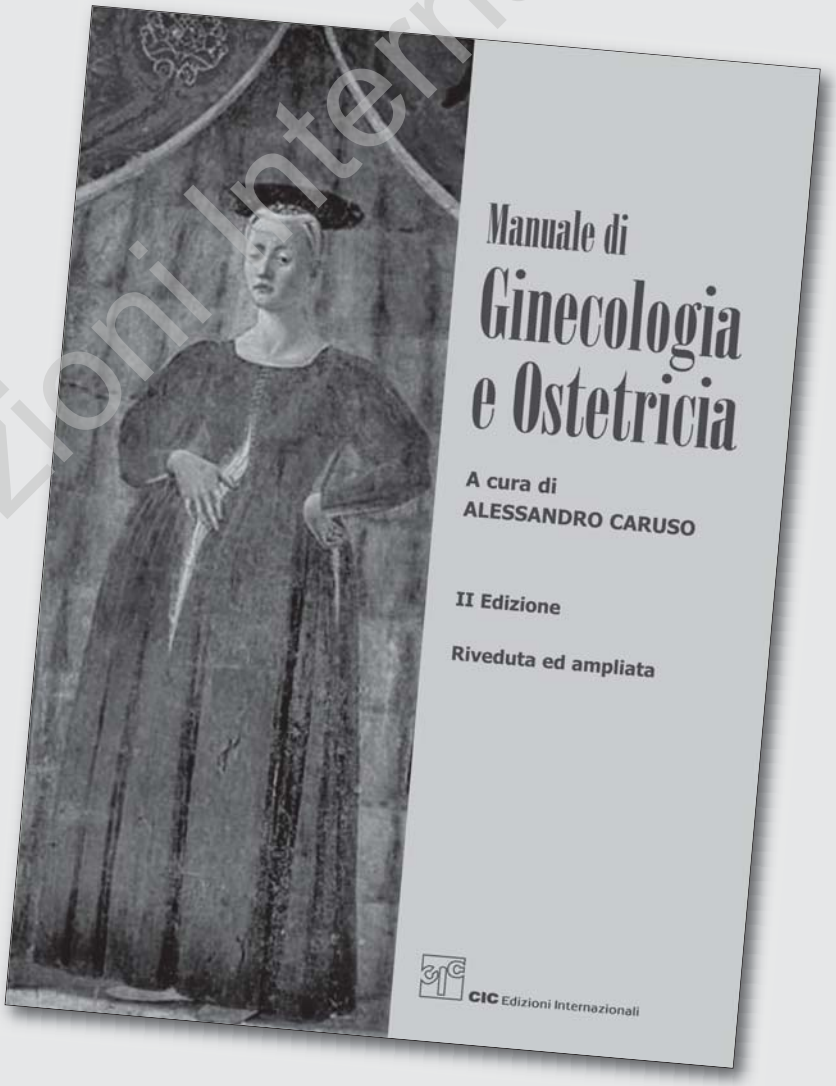

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Peritoneal tuberculosis in the differential diagnosis with peritoneal carcinomatosis: case report and literature review

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ABSTRACT

Peritoneal tuberculosis in the differential diagnosis with peritoneal carcinomatosis: case report and literature review.

Tuberculosis is a severe public health problem in developing countries, but it is taking on the characteristics of a global epidemic. By virtue of migration flows, in fact, we are observing a resurgence of this disease in western countries, in all its forms including the genital one.

The problem became more serious with the emergence of multidrug-resistant mutant (MDR) strains of Mycobacterium Tuberculosis.

In this paper we describe a case of peritoneal tuberculosis, whose diagnosis was histologically made after laparoscopic examination.

Laparoscopy proved crucial for the differential diagnosis with peritoneal carcinomatosis, particularly following the discrepancy in the results provided by ultrasound and Computerized Tomography (CT) examinations.

These two diseases are, in fact, very different in their pathogenesis, but above all in their treatment options and prognostic outcomes.

Genital tuberculosis is a major cause of severe tubal disease leading to infertility. Unlike pulmonary tuberculosis, its clinical diagnosis is difficult because in most of cases genital tuberculosis can be asymptomatic or have a large variety of clinical features.

Key words: tuberculosis, multidrug-resistant mutant strains, laparoscopy, infertility, HIV, peritoneal carcinomatosis.

SOMMARIO

Peritoneal tuberculosis in the differential diagnosis with peritoneal carcinomatosis: case report and literature review.

La Tubercolosi (TBC) rappresenta un serio problema di salute pubblica nei paesi in via di sviluppo, ma sta assumendo le caratteristiche di un'emergenza globale. A causa dei flussi migratori, infatti, stiamo assistendo alla recrudescenza della malattia nei paesi occidentali in tutte le sue forme, inclusa quella genitale. La questione è divenuta più grave con l'emergere di ceppi tubercolari mutanti multi-resistenti.

In questo lavoro descriviamo un caso di tubercolosi peritoneale, la cui diagnosi è stata posta istologicamente dopo osservazione laparoscopica.

La laparoscopia si è dimostrata cruciale per la diagnosi differenziale con la carcinosi peritoneale, particolarmente a seguito della discrepanza nei risultati forniti dall'esame ecografico e dalla Tomografia Computerizzata (TC).

Tubercolosi peritoneale e Carcinosi peritoneale sono infatti molto diverse tra loro nella patogenesi, ma soprattutto nelle opzioni terapeutiche e nella prognosi.

La tubercolosi genitale è una causa maggiore di patologia tubarica severa e conseguente sterilità. A differenza della forma polmonare, la sua diagnosi clinica è difficile poiché nella maggior parte dei casi si tratta di un quadro asintomatico o che comunque si associa ad una grande varietà di presentazioni cliniche.

Parole chiave: tubercolosi, ceppi mutanti multi resistenti, laparoscopia, sterilità, HIV, carcinosi peritoneale.

INTRODUCTION

Tuberculosis, caused by Mycobacterium Tuberculosis, represents a severe health problem in developing countries.

In 1994 World Health Organization (WHO) declared Tuberculosis a global epidemic: it affects about 8 millions people every year, causing 2 millions deaths; most of these are women from developing countries (1,2).

Concomitant Human Immunodeficiency Virus (HIV) infection, particularly in Sub-Saharan Africa, worsened this problem (2).

Increasing in migration flows from high risk towards low risk areas determined a greater incidence of Tuberculosis in North America and in West Europe (2). This prob-

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lem became more serious with the emergence of multidrug-resistant mutant (MDR) strains of Mycobacterium Tuberculosis (2).

Risk factors for Tuberculosis are represented by immigration, low socioeconomic status, close contact with affected individuals, immunosuppression, HIV infection (3,4).

Peritoneal tuberculosis is a particular form of abdominal tuberculosis that involves mainly the intestinal tract, liver, spleen, female genital tract, omentum, parietal and visceral peritoneum (5).

Peritoneal tuberculosis interests about 1-2% of all individuals affected by tuberculosis (6).

Female genital tuberculosis appears with a great variety of clinical features: primary or secondary infertility, menstrual irregularities, chronic pelvic pain, pelvic mass appearance; in addition, it could be associated with systemic symptoms such as fever, weight loss and anorexia (7,8).

Fallopian tubes are the most frequently involved organs, followed by endometrium, ovary and less frequently cervix, vagina and vulva (8,9).

Genital tuberculosis is a major cause of infertility, above all in developing countries; in fact, it could determine tubal obstruction, peritubal, pelvic, abdominal (10,11), periepathic adhesions (Fitz-Hugh-Curtis Syndrome) (12).

Genital tuberculosis, in addition, could cause endometrial atrophy, that in turn can lead to Asherman's Syndrome and to uterine cavity constriction (13).

Even if genital tuberculosis can be sexually transmitted, most of cases follows to hematogenic, lymphatic, or abdominal diffusion (8).

CASE REPORT

In 2011 March comes to our attention an Ethiopian woman with a negative obstetrical anamnesis. The admitting diagnosis is pelvic pain associated with Douglas Pouch fluid collection.

Remote pathological anamnesis is negative for noteworthy diseases, however it remains uncertain due to difficulties in communication related to language.

Patient reports weight loss and worsening pelvic pain in the last three months, associated with dysuria and white mucus-like discharge during urination; she also reports intermittent fever and profuse night sweating.

At the first pelvic examination there is not any atypical vaginal discharge; uterine corpus is mobile and painless; adnexal regions and Douglas Pouch appear normal.

Hemochrome shows a lymphopenia, while the other parameters are normal; for this reason we ask for an infectivological consulting, suspecting an HIV infection. At the end of infectivological examinations, on the contrary, patient results negative for HIV, HCV and HBV infections.

Urine examination reveals a mild bacteriuria (5284 n°/μL); for this reason and on the basis of antibiogram, we start an antibiotic therapy with ceftriaxone.

At ultrasonographic pelvic transvaginal examination uterus and adnexal regions appear normal, but a large fluid collection in Douglas Pouch is seen.

Assays for ovary cancer markers show a significant increase in CA125 levels (967 mIU/ml), therefore we ask for a Computerized Tomography (CT) abdominal scan.

CT scans, performed with and without a contrast medium, reveals the presence of two pelvic solid masses, in the context of both the adnexal regions; these two masses shows an irregular morphology, have a diameter of about 4 cm, are adherent to parietal peritoneum and seem proliferative lesions. CT also reveals the presence of ascites and of some solid carcinomatosis implants on greater omentum surface. This result, together with the significant increase in CA125 levels, lead us to suspect an ovarian cancer. Therefore we decide to perform a laparoscopy.

Laparoscopic observation shows pelvic parietal peritoneum and adnexal structures covered by a fine white punctate; ovaries appear normal; however, an outflow of caseous-like material from tubal ostium is observed. On the basis of this report, we begin to suspect a tubercular origin of disease, therefore some ovarian biopsies and biological materials' sampling are performed.

Histological examination of ovarian fragments reveals a chronic granulomatous in-

flammation associated with caseous necrosis and a fair number of tubercle bacilli (Ziehl-Neelsen positive). TBG Gold immunological assay is then performed, which results positive; bacterial nucleic acids essay by PCR in peritoneal fluid is negative instead, as direct microscopy on tubal caseous-like material, after Ziehl-Neelsen colouring.

In order to detect the primary origin of genital tuberculosis thoracic XRay and CT are performed.

The first appears normal. CT, on the contrary, shows in left perihilar region some radiotransparent little areas, delimitate by radiopaque margins, worthy of further examinations; a left mild pleural effusion is seen, together with fibrotic dysventilated areas in right apical region; however, neither secondary parenchymal lesion nor enlarged lymph node is observed.

Finally, patient is transferred to Infectious Diseases Unit in order to continue diagnostic course and to begin a specific medical treatment.

DISCUSSION AND CONCLUSIONS

In this paper we describe a case of peritoneal tuberculosis mimicking a malignant ovarian cancer, in order to emphasize the importance of obtaining a definitive histological diagnosis, in women with suspect advanced ovarian cancer, before they start chemotherapy.

Genital tuberculosis (GTB) is a major cause of severe tubal sequelae that often lead to infertility.

Unlike pulmonary tuberculosis, clinical diagnosis of GTB is difficult because in most of cases it is asymptomatic or it could have a great variety of clinical features.

Routine laboratory values are of poor utility in the diagnosis. Due to paucibacillary nature of GTB, cultures for Mycobcterium Tuberculosis and histopathological examination (HPE) are often associated with low detection rates. PCR appears useful sometimes in the early diagnosis and when a diagnostic confirmation is needed in clinically suspected cases (14).

It is correct to affirm that no single test is able to reveal all the characteristics of GTB; it is therefore necessary a combination of tests in order to increase the detection rate. Peritoneal tuberculosis can often be confused with peritoneal carcinomatosis; CT could be crucial in the differential diagnosis between these two diseases, that are very different in their pathogenesis but above all in their corresponding treatment options and prognostic outcomes. Visualization of smooth peritoneum with minimal thickening, in fact, suggests a Peritoneal Tuberculosis (PT); on the contrary, nodular implants and irregular peritoneal thickening suggest a Peritoneal Carcinomatosis (PC) (15).

Tuberculosis is taking on the characteristics of a global epidemic, we are observing in fact a resurgence of this disease in all its forms, including the genital one.

It becomes therefore necessary that gynecologist becomes able to make the diagnosis and to identify readily GTB signs, since its differential diagnosis is not always easy.

For these reasons it's necessary to have a complete knowledge not only of the clinical features but even of appropriate diagnostic tools, in order to come to a correct diagnosis and to a suitable therapeutic choice, for a particular group of patients who often shows a low compliance.

There are not clinical signs, nor laboratory parameters, nor radiological findings that can be considered pathognomonic for peritoneal tuberculosis, so it can be easily confused with peritoneal carcinomatosis and with advanced ovarian cancer.

Abdominal tuberculosis requires a conservative medical management by means of anti-tubercular therapies. On the contrary, ovarian cancer obviously requires a radical surgical approach, together with chemotherapy and radiotherapy.

Is then of great importance to know those diseases mimicking ovarian cancer, since their misdiagnosis could lead to unacceptable delays in diagnostic course, but above all to vain overtreatments or to incorrect therapeutic choices.

Finally, in the management of these cases laparoscopy proves crucial. In fact, in doubt cases it permits to obtain multiple samples on which simultaneously performing different examinations till the definitive diagnosis of GTB is made.

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Role of hysteroscopy in endometrial osseous metaplasia diagnosis: case report and literature review

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ABSTRACT

Role of hysteroscopy in endometrial osseous metaplasia diagnosis: case report and literature review.

In this paper we describe a case of endometrial osseous mataplasia, whose diagnosis was histologically made after ultrasonographic and hysteroscopic observation.

Osseous metaplasia of the endometrium is an uncommon disease, with controversial etiology and unclear pathogenesis. However, it believes that its actual incidence may be underestimated due to the lack of clinical experience and to long asymptomatic phase of the disease itself.

This case report also puts emphasis on the need to consider this disease in the differential diagnosis above all of malignant mixed Müllerian tumor, in order to avoid diagnostic errors that could lead to unnecessary hysterectomies.

To this end, in addition, we reaffirm the validity of the hysteroscopic technique in the diagnosis and treatment of this disease.

Key words: metaplasia, connective tissue, bone tissue, abortion, malignant mixed Müllerian tumor, hysteroscopy, hysterectomy.

SOMMARIO

Ruolo dell'isteroscopia nella diagnosi di metaplasia ossea endometriale: caso clinico e revisione della letteratura.

In questo lavoro descriviamo un caso di metaplasia ossea endometriale, la cui diagnosi è stata posta istologicamente a seguito di esame ecografico ed isteroscopico.

La metaplasia ossea dell'endometrio è un quadro patologico non comune, ad etiologia ancora controversa e a patogenesi non del tutto chiara. Si ritiene attualmente che la sua reale incidenza sia sottostimata, a causa della carenza di esperienza clinica specifica e della lunga fase asintomatica.

Il caso clinico descritto pone l'accento sulla necessità di prendere in considerazione questa patologia nella diagnosi differenziale col tumore misto mülleriano maligno, al fine di evitare errori diagnostici che condurrebbero ad interventi radicali non necessari, come l'isterectomia.

A tal proposito si conferma la validità della tecnica isteroscopica non solo nella diagnosi ma anche nel trattamento della metaplasia ossea endometriale.

Parole chiave: metaplasia, tessuto connettivo, tessuto osseo, aborto, tumore misto mülleriano maligno, isteroscopia, isterectomia.

INTRODUCTION

Osseous metaplasia of endometrium is an uncommon disease characterized by transformation of connective tissue in bone tissue. This process is different from both ossification and endometrial calcification consequent to embryonic or fetal bone tissue persistence after abortion.

Most of women with endometrial osseous metaplasia are 20 to 40 years old (1), but some cases in menopausal age are documented (2).

Osseous metaplasia is very infrequent (incidence of 3 cases on 10.000 women) (3,4). Less than 100 cases are reported in literature, and 9 of these in India (5-9).

More than 80% of patients affected by this disease present previous pregnancy failures (5-7, 10-12). An history of abortions or third trimester fetal deaths is indeed considered the most common risk factor for endometrial osseous metaplasia.

The direct implantation of retained fetal parts in uterus is considered the responsible factor for etherotopic bone tissue formation.

In literature, however, rare cases in nulliparous women or women with a single early abortion are documented. In these cases it obviously couldn't be hypothesized bone tissue formation. A possible explanation could be the "true" metaplasia, in which endometrium

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changes its characteristics in order to adapt to a new environment, as in case of chronic inflammation (dystrophic osseous metaplasia). On the other hand, even fetal bone retention can cause a chronic endometrial inflammation, leading to a secondary osseous metaplasia (13-15).

For this reason, these two different processes can't be always clearly distinguished.

On the basis of evaluation of cases reported in literature, it seems that the gap between pregnancy failure and endometrial ossification detection can vary from 8 weeks to 23 years (16-18).

Despite clinical feature can include many symptoms and signs as vaginal discharge, menstrual irregularities, abnormal uterine bleeding, dysmenorrhea, pelvic pain, dyspareunia, bone fragments release by menstrual blood or vaginal discharge, the reason that more frequently leads women to see their gynecologist is secondary infertility (1-18).

CASE REPORT

In 2011 April comes to our attention a 44 years old woman, with a clinical history of two previous consecutive pregnancy losses in 1990 and 1991 and one subsequent term pregnancy with spontaneous vaginal delivery.

The patient is positive for HCV- e HIV-infection, with HIV-related renal failure and neuropathy, HCV-related chronic epatopathy; in addition she suffers from anxious-depressive syndrome, with an history of many major depressive episodes.

Pelvic examination appears normal.

Ultrasonographic transvaginal examination reveals the presence of an hyperecogenic area in uterine cavity (LD 14 mm, APD 6 mm); pouche of Douglas and adnexal regions are normal.

On the basis of US results we decide to perform a diagnostic office hysteroscopy, using a continuous flow office hysteroscope (Karl Storz Endoscopy).

Hysteroscopic examination shows an irregular uterine cavity for the presence of a white-yellow neoformation, made of bone spicules, arising from posterior wall and extending towards the cavity, hard and with jagged margins; tubal ostia are both visualized; endometrium, isthmus and cervical canal appear normal.

Multiple biopsies are performed. Histologic examination shows secretive endometrial fragments; one of these includes bone tissue and is finally related to endometrial osseous metaplasia without atipies.

The neoformation is therefore excised by bipolar resectoscope (Karl Storz Endoscopy).

DISCUSSION AND CONCLUSIONS

Endometrial osseous metaplasia is an uncommon disease, with controversial etiology and unclear pathogenesis. However, it believes that its actual incidence may be underestimated due to the lack of clinical experience and to long asymptomatic phase of the disease itself (1-18).

Parente et al. analyzed by DNA genotipization some bone fragments found in uterine cavity, in order to clear if they resulted from "true" metaplasia or from previous abortion, or both.

DNA was extracted from blood and from bone fragments, then a genotipization was made.

The results gave the same DNA profile for osseous samples and for corresponding maternal blood, thus confirming the origin from "true" metaplasia, despite the fact that all women included in the study presented an history of abortions. This outcome was completely unexpected and very different from what literature suggests (19).

Ultrasonographic suspect and successive hysteroscopic confirmation are essential for diagnosis of endometrial osseous metaplasia.

Formerly, in most of cases diagnosis was made after bone tissue excision by endometrial curetting, then an hysterectomy was performed.

Nowadays, the correct management include diagnosis by transvaginal ultrasonographic and hysteroscopic examination, followed by laparoscopy-assisted hysteroscopic excision. The advantages include the simultaneous visualization of abdominal and uterine cavities, a reduced invasiveness and reduced costs (20).

Endometrial osseous metaplasia could be a very rare cause of infertility. Hysteroscopic approach is effective also in order to restore fertility, often in a little time. In fact, when bone tissue is removed, regardless of metaplasia area size, normal pregnancy is possible.

However, if osseous metaplasia is deep, during hysteroscopic excision it could more easily occurr an uterine perforation, a complication that should be considered in these cases (21).

Finally it's important to emphasize the fact that osseous metaplasia can be easily misdiagnosed, because of its poor incidence. This disease could be therefore always considered in the differential diagnosis in those patients with an US image similar to that of an Intra-Uterine Device (IUD) (22). In this case the differential diagnosis, in addition to IUD, has to include malignant mixed Müllerian tumor, theratoma, endometrial tuberculosis, fetal bone tissue retention.

This case report puts the emphasis on the rarity of this disease, but also on the need to consider endometrial osseous metaplasia in the differential diagnosis of malignant mixed Müllerian tumor above all, in order to avoid diagnostic errors that could lead to unnecessary hysterectomies.

To this end, in addition, we reaffirm the validity and the safety of hysteroscopic technique in the diagnosis and treatment of this disease.

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A family planning programme as a solution to back-street abortion in a Congolese community

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ABSTRACT
A family planning programme as a solution to back-street abortion in a Congolese community.

Introduction. We performed the study in the community of Kadutu, in Bukavu (Democratic Republic of Congo). The aim was to evaluate the reduction of back-street abortions thanks to the family planning service activated by the Medical Centre St. Vincent.

Methods. We compared the phenomenon of abortion in year 2007, when no service offered a contraceptive method and the year 2010, three years after the introduction of the service with availability of contraceptive methods. These are the objectives:

1 - To calculate the risk of abortion and its complications in a population without knowledge and access to contraceptive methods.

2 - To control the evolution of abortion and its complications after the introduction of the service.

3 - To evaluate the understanding of women, who had had a back-street abortion, about contraceptive methods.

4 - To evaluate the preference for a specific contraceptive method.

Results. 1) The introduction of the family planning service decreased the number of abortions and its related complications. 2)Women, who had had abortion before, improved their knowledge of contraceptive methods. 3) Oral contraceptives are the favourites, followed by the injectable ones.

Conclusion. Abortion is five times higher in people who ignore or don't have the chance to access to contraceptive methods.

Key words: family planning in Africa, abortion in Africa.

SOMMARIO
Un programma di pianificazione famigliare quale soluzione all'aborto illegale in una comunità congolese.

Introduzione. Lo studio è condotto nella comunità di Kadutu, comune di Bukavu (Repubblica Democratica del Congo) per valutare l'efficacia del servizio di pianificazione famigliare attivato dal Centro Medico San Vincenzo nel ridurre il numero degli aborti illegali.

Metodi. Abbiamo confrontato il fenomeno dell'interruzione volontaria di gravidanza (IVG) nell'anno 2007, anno durante il quale nessun servizio offriva metodi contraccettivi e l'anno 2010, tre anni dopo l'introduzione del servizio con disponibiltà di metodi contraccettivi. Questi gli obiettivi:

1 - Calcolare il rischio di IVG e delle sue complicanze in una popolazione senza conoscenze e possibilità di accesso ai metodi contraccettivi.

2 - Controllare l'evoluzione delle IVG e delle complicanze relative dopo l'introduzione del servizio.

3 - Valutare la conoscenza dei metodi contraccettivi presso le donne che hanno praticato aborti illegali.

4 - Valutare la preferenza tra i contraccettivi proposti.

Risultati. 1) L'introduzione del servizio di pianificazione famigliare ha ridotto il numero delle IVG e le complicanze relative. 2) La conoscenza dei metodi contraccettivi è nettamente migliorata tra le donne che hanno avuto una interruzione volontaria della gravidanza. 3) La preferenza è per i contraccettivi orali seguita da quelli iniettabili.

Conclusioni. La pratica di interrompere una gravidanza è 5 volte più elevato in una popolazione senza conoscenze e possibilità di accesso ai metodi contraccettivi.

Parole chiave: contraccezione in Africa, interruzione volontaria di gravidanza in Africa.

INTRODUCTION

In the Democratic Republic of the Congo, as well as in other thirty-nine of the fifty countries of Africa, the law prohibits the voluntary termination of pregnancy, authorizing it just for therapeutic purposes (1); moreover in those countries sexual education and con-

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traceptive methods are usually very limited. Formal statistics about abortion don't exist because it is an illegal practice. Back-street abortions are very dangerous and sometimes even life-threatening: in 2003 48% of abortions worldwide were considered unsafe and more than 97% of them happened in developing countries (2).

We could get datas, certainly incomplete, relative to our Congolese community, from municipal books (3), from annual reports of the Kadutu Health District (4) and from Medical Centre St. Vincent of Bukavu (5,6).

These are the statistics of year 2007: 47 newborns and 7 fetuses were picked up from the Kadutu's sewer system; in the same year we admitted to hospital 126 cases of complications after back-street abortion, including 3 uterine perforations, two of them requiring hysterectomy. In the Health District 6 deaths were reported. The annual report, that centralizes all medical datas of the Health District, indicates 289 cases of abortion that were examined in the different surgeries of the District in the year 2007. In 2010 3 fetuses were picked up (decrease of 93.7%) while no newborn was picked up. 15 cases of complications due to back-street abortion were admitted at the Medical Centre St. Vincent (decrease of 88.1%); in all 55 cases were indicated in the annual report of the District. One death after abortion was reported in the community (decrease of 83.4%).

In the Kadutu District the 43.6% of the complications from abortion are admitted to the the Medical Centre St. Vincent. So we decided to organize a service of family planning. The aim is to provide people with necessary information about birth control, to place contraceptive methods at population's disposal, to inform about the risks of back-street abortion. At a distance of 3 years since the introduction of the service, the study aims are the following:

1. To outline the socio-demographic characteristics of women who practise back-street abortion;
2. To weigh the influence of the family planning service on the cases of voluntary abortion in the population of the District;
3. To point out the knowledge about responsible procreation of women who did back-street abortion;
4. To find out the preferences for the different contraceptive methods.

The aim is to build a basis for coming wider and more elaborate studies, to demonstrate the importance of the family planning to prevent back-street abortion, to provide politicians with an effective solution to this severe problem.

METHODS

The Kadutu District, where this study was carried out, is one of four municipal districts of Bukavu. The estimated population is about 400,000 people, including 160,000 women of childbearing age. The Medical Centre St. Vincent is a medical facility MSAADA-owned, a Congolese non-governmental organization (ONG), supported by the Italian Onlus " Con Vista Sul Mondo" ("With sight on the world"). This ONG has been working since 15 years and intends to take care of poor people, that can't allow themselves public hospitals or private clinics.

The medical centre is provided with surgeries, 26 in-patients beds, a operating theatre and a delivery room. Moreover it is a reference for medical education throughout the District. The staff is composed by doctors, nurses and administrators. The family planning service was set up in year 2008.

This study compares the situation of abortions in 2007 and in 2010 according to the following characteristics:

– residence in Kadutu;
– registration in municipal books;
– registration Medical Centre St. Vincent's books;
– complete case history.

The residence in Kadutu, where the Medical Centre St.Vincent is situated, is the first inclusion method, because the population of Kadutu is our target. We got data toghether from case hystories, disease books, municipal books, annual summaries of epidemiological reports of the central office in Kadutu. We sought for the following characteristics:

– Age: range 14-18, 19-23, 24-28, >28;
– Level of education: none, primary

school, secondary school (pupil), university (student);
– Occupation: none, trader, pupil, student;
– Marital status: married, single, divorced;
– Knowledge of contraceptive methods;
– Choice of contraceptive methods.

RESULTS

During the year 2007, 289 back-street abortions and 7 cases of newborn abandonment have been registered in the Kadutu Health District. 48 cases have been excluded from the sample (in 37 cases only fetuses were found because their mothers were hidden to avoid the process, 8 case histories were incomplete, 4 cases came from other municipalities). 241 cases were selected for the study. In 235 case (Fig. 1) there were complications (97.5%): 125 retentions of chorionic tissue (53%), 42 post-abortion endometritis (18%), 52 hemorrhagic shock (22%), 5 uterine perforations (2%), 11 deaths (5%).

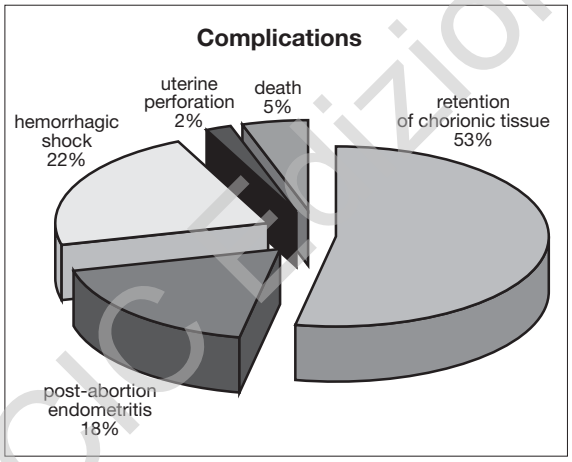

Figure 1. Complications after IVG in 2007.

This is the activity of the family planning service from 2008 right to the end of 2010. 52 radio programmes about sex education, 6 lectures in three of the main advanced school of the Kadutu municipality, where most of the girls of the district study, and involving also boys, that are often neglected in these programmes (7).

3613 people got access to the family planning service and adopted one of the contraceptive methods proposed (Fig. 2): 893 couples chose injectable hormones (24.7%), 1400 oral contraception (38.7%), 7 IUD (0.2%), 539 male condom (14.9%), 18 contraceptive implants (0.5%), 17 tubal sterilization (0.5%), 739 natural methods (20.5%).

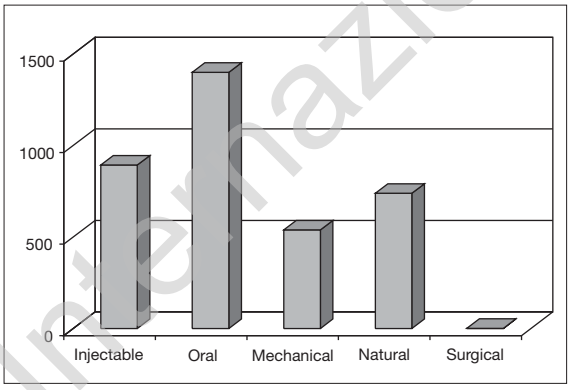

Figure 2. Contraceptive methods.

As regards back-street abortions, in year 2010, 56 cases have been reported in the annual relation of the central office of the Bukavu health department. 8 cases have not been included (4 were out of the District, 3 fetuses were taken without identifying who did abortion, in one case there wasn't a complete documentation). 24 complications (42.9%) have been registered at the Medical Centre St. Vincent.

So among the 56 cases of abortion, we included 48 cases and complications happened in 37 of them (77.8%); particularly there were 5 endometritis (13.5%), 3 uterine perforations (8.1%), 16 retentions of chorionic tissue (43.2%), 13 hemorrhagic shocks (5.1%).

Sociodemographic characteristics

The distribution of back-street abortion is the following:

– *Age groups*

Year 2007 (Fig. 3): range 19-23 years is in the majority with 119 cases (49.4%), followed by range 14-18 years with 58 cases (24%), range 24-28 years with 40 cases (16.6%) and at last range >28 years with 24 cases (10%).

Year 2010: the proportion is unchanged: range 19-23 years is in the majority with 23 cases (62.2%), followed by range 14-18 years with 8 cases (21.6%), range 24-28 years with 4 cases (10.8%) and at last range > 28 years with 2 cases (5.4%).

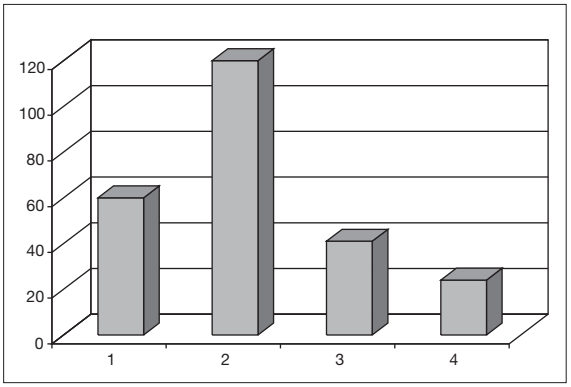

Figure 3. Age groups, year 2007: 1=14-18; 2=19-23; 3=24-28; 4=>28 years.

– *Level of study*

Year 2007: the number of women who studied until secondary (classical) studies is in the majority with 133 cases (59.4%), followed by the group of women who had been to university with 72 cases (32.1%). Women who had attended only the primary school follow with 13 cases (5.8%) and at last there were 6 women who never had gone to school (2.7%). 17 cases weren't included because the education level wasn't clearly indicated in the registration (the cases selected are 224).

Year 2010: the number of women who had been to university is in the majority with 14 cases (37.8%), followed by the the groups of women who studied until secondary studies and who never attended school with 8 cases each (21.6% each) and at last the women who studied until the primary school with 7 cases (19%).

– *Job*

Year 2007 (Fig. 4): the category of the students (university) is in the majority with 98 cases (40.7%), followed by the traders with 73 cases (30.3%), the pupils (secondary school) with 54 cases (22.4%) and at last the unemployed with 16 cases (6.6%).

Year 2010 (Fig. 5): the category of the students is in the majority with 13 women (35.1%), followed by the traders with 10 cases (27%), the unemployed with 8 cases (21.6%) and at last the pupils with 6 cases (16.2%).

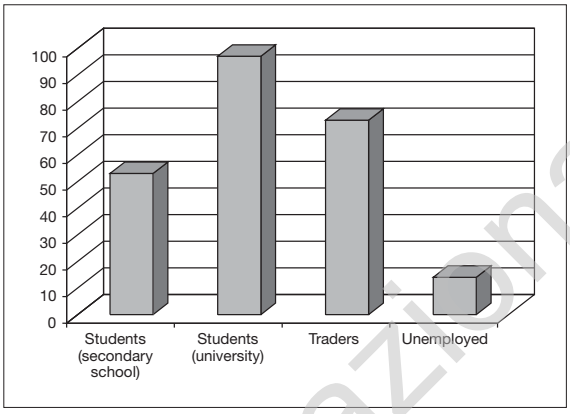

Figure 4. Job year 2007 (see text).

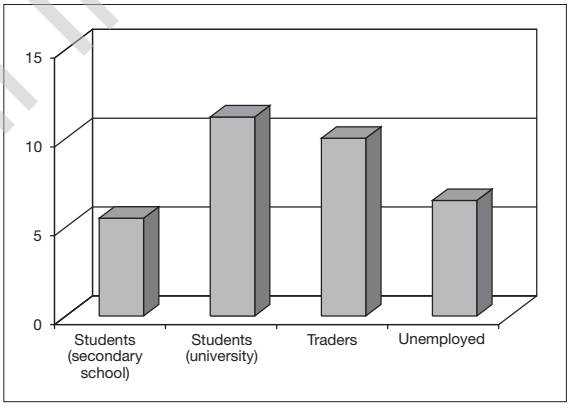

Figure 5. Jobs, year 2010 (see text).

– *Civil status*

Year 2007: the unmarried women were 166 (68.9%) while the married ones were 73 (30.3%) and at last the divorced with 2 cases (0.8%).

Year 2010: the unmarried women were 29 (78.4%) while the married ones were 8 (21.6%).

– *Knowledge of contraceptive methods*

Year 2007: the 19% of women declared a vague knowledge of contraceptive methods, while the 81% had no information at all.

Year 2010: the 87% of women declared a good knowledge of contraceptive methods.

DISCUSSION

In spite of the limits due to the secrecy of the practice, our data showed that 289 cases have been registered in Kadutu District during the year 2007. We compared them with the 56 cases registered during 2010 and we noticed an interesting reduction of abortions of 81%. In 2007 there weren't services of sex education and family planning and contraceptive methods were unavailable in all the district. The Medical Centre St. Vincent introduced these services in 2008 and awakened people through radio-conferences and TV-debates to responsible procreation and to complications related to abortion. A counselling centre for family planning that provides also contraceptive methods was opened. The cases registered at the hospitals of our Health District are mainly complications arisen during or after abortion. The complications are frequent because abortions are performed secretly, with poor hygienic conditions, by unskilled hands.

Our data show that chorionic tissue retention is the most frequent complication with 125 cases (53.2%) in 2007, while other work groups (8) considered it un uncommon event. This difference may be explained considering the different ways of collecting datas.

Women come to the attention of the Medical Centre St. Vincent mostly for the following reasons: metrorrhagia or infection. Metrorrhagia evolved in hemorrhagic shock in 52 cases (22.1%). Shock is the first cause of post-abortion mortality in our study; some hospitals of Kadutu Health District didn't have a blood bank in year 2007. Post-abortion endometritis,42 cases (17.9%), are the third cause of complication and the second cause of post-abortion death. Uterine perforations following endouterine procedures are another complication found in almost 2.1% of cases.

These data induced us to start a family planning service. The aim is to educate,to inform the population about different contraceptive methods and to place them at people's disposal to avoid unwanted pregnancies and back-street abortions. The result is that, during the year 2010, 3616 people used a contraceptive method. Abortion, after the informative campaign, registered a decrease of 81% as the complications of abortion (55 cases against 289). Chorionic tissue retentions (43.2%) remain at the first place of the list of complications, followed by hemorrhagic shock (35.1%); there were not deaths.

The age-distribution of women who had an abortion remains unchanged in 2007 and in 2010: age-range 19-23 years, age of the universitary studies, is the most represented. This is the period where people are sexually more active, where girls discover the freedom and the ease of the approach to the male sex. The second range is 14-19 years, when girls attend secondary school and generally start having their first sexual intercourses. The ignorance or the poor knowledge of reproduction phisiology cause unwanted pregnancies.

Abortions occur more frequently during holidays or during the first trimester of the school calendar; these observations suggest that pregnancies start frequently during the summer holidays.

Women between 24 and 28 years are usually married and live in a family. In this cases they want to have an abortion because pregnancy is unwanted and unplanned. Moreover bad informations about contraceptive methods and the absence of qualified services, are the causes of the cases of abortion observed in women over 24 years.

As regards to the education level, the group of women who studied until secondary (classic) school is the most numerous with 59.4% in 2007, while in 2010 the first group is that of women who studied until the universitary level with 32.1%.

As regards work, the students are the largest group; they are sexually active but they rarely use contraceptive methods. The second group is that of female traders, who often travel for many days faraway from their houses. In 2007 the category of pupils (secondary school) is at the third position with 22.4%; in 2010 it is at the fourth position with 16.2% after the category of women without a job. We retain that this reduction is due to our sex-education sessions in secondary schools and to the opening of consulence services for the responsible procreation also to not married girls (at the beginning our consulence activity was only for married or engaged couples).

As regards civil status, single women are at the first position representing the 68.9% in 2007 and the 78.4% in 2010; they are usually students and pupils. In the population that we study, in 2007 only the 19% had knowledge of contraceptive methods against the 87% in 2010. The number of back-street abortions changed from 289 (in 2007) to 55 (in 2010), with a decrease of 81%, mainly thanks to the activity of the family planning service.

Among people that use contraceptive methods, they prefer oral contraceptives (38.7%). This method is followed by the injectables ones. Natural methods are used by a considerable number of women (20.5%) and are at the third place, in spite of the high error risk and the necessity of good knowledge of the menstrual cycle. The use mechanic or barrier methods is rather poor.

CONCLUSION

We conducted a study in Kadutu, municipality of Bukavu (Democratic Republic of Congo). The aim was to evaluate the influence of the family planning service and the availability of contraceptive methods offered by the Medical Centre St. Vincent on the termination of pregnancy. We compared cases collected during 2007, when contraceptives were mostly unavailable, and during 2010, when the family planning service has been working since three years. At the end of our study, we drew the following conclusions:

1. The introduction of the family planning service reduced five times the practice of termination of pregnancy;
2. Women who did abortion improved their knowledge of contraceptives (passing from 19% to 87%). So we can deduce the knowledge of contraceptive methods of the population and to justify the reduction of abortion practice;
3. Women prefer particularly the oral contraceptives, followed by the injectable ones.

The study demonstrates that the availability of contraceptive methods have a positive influence on back-street abortion, in line with what has been already proposed by OMS (9), by authoritative humanitarian agencies (2,8) and by experiences started in Congo and in other countries in Sub-Saharan Africa (7,10,11).

The study gives to the Congolese health managers important elements to promote the use of contraceptive methods, considering and respecting female preferences, as proposed by many international organizations (10).

In defence of women's health, we wish coming changes of laws about abortion and reproductive health (12,13). Back-street abortion, according to OMS, is responsible of the 13% of the maternal deaths all over the world, 67000 per year. The risk of dying of unsafe abortion in devoloping coutries is 1 every 250 procedures, while in developed countries is 1 every 3700 procedures. Complications that require medical intervention are estimated between 10 and 50% (8).

For Western health workers, who nowadays deal with a more and more considerable immigration from Africa, this study help them to know the reality of the countries of origin and to better organize preventive and effective measures (14).

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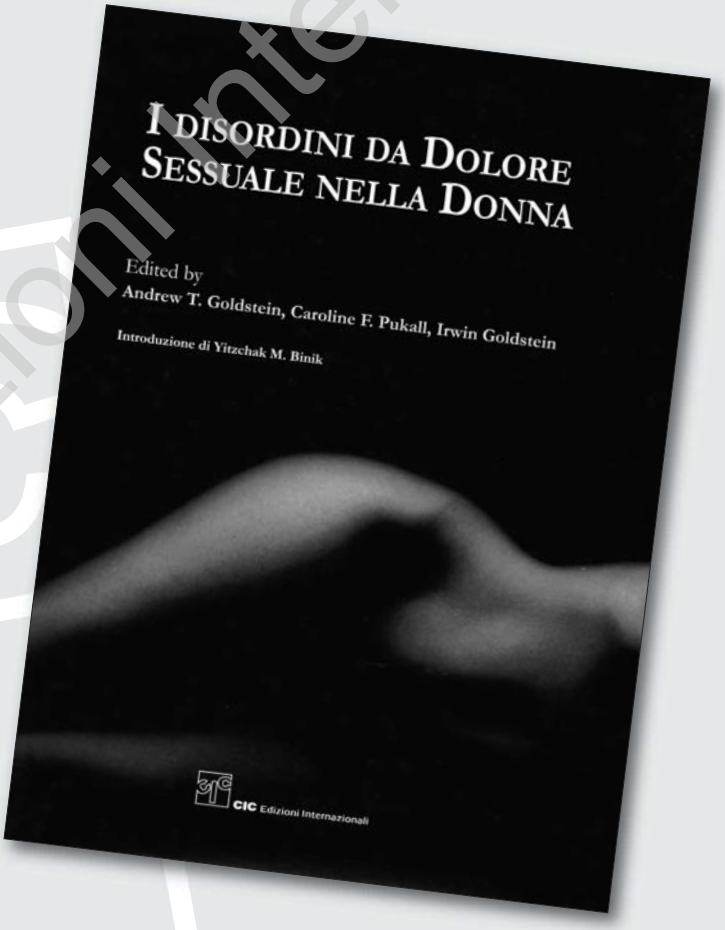
I DISORDINI DA DOLORE SESSUALE NELLA DONNA

Introduzione di
Yitzchak M. Binik



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Paget's disease of the vulva. Case report

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ABSTRACT

Paget's disease of the vulva. Case report.

Paget's disease of the vulva is a rare, chronically recurrent neoplastic disease of the skin and cutaneous adnexa, affecting postmenopausal women and characterized by long lasting local discomfort. It is rarely a secondary manifestation of an adenocarcinoma arising from other adjacent sites. Histological examination of multiples specimens is necessary to exclude invasion to deeper layers and the malignant pattern. Wide surgical excision is the treatment of choice, even if an high rate of recurrences must be expected. In recurrent cases, topical imiquimod applications represent a valid option with satisfactory cure rates.

Key words: Paget, Paget's disease, vulvar Paget, vulva.

SOMMARIO

Malattia di Paget della vulva. Caso clinico.

La malattia di Paget della vulva è una condizione neoplastica, cronica e recidivante, della cute e degli annessi cutanei, riscontrabile in postmenopausa e caratterizzata da una lunga sintomatologia locale. Raramente rappresenta una localizzazione secondaria di un adenocarcinoma ad insorgenza da sedi anatomicamente contigue. Lo studio istologico di multipli campioni bioptici è necessario per escludere l'invasione ai piani profondi e le caratteristiche di malignità. Il trattamento elettivo è rappresentato da una ampia escissione chirurgica, anche se una alta probabilità di recidiva deve essere prevista. Nei casi recidivanti, l'applicazione locale di imiquimod rappresenta una valida opzione, con risultati soddisfacenti in termini di guarigione.

Parole chiave: Paget, malattia di Paget, Paget vulvare, vulva.

INTRODUCTION

Paget's disease of the vulva is a rare, locally recurrent condition that accounts for almost 1% of all vulvar malignancies. Most of its clinical and pathological aspects are still far from being clearly clarified: natural course of the disease, prognostic pathological patterns and optimal options of management represent interesting open questions for the clinician. A significant clinical case is reported and taken as a useful example to trace and summarize practical and updated guidelines.

CLINICAL CASE

A post-menopausal Caucasian woman attended gynecological consultation for long-lasting pruritus vulvae, burning and pain, not responding to self-administered topical aspecific preparations, including antifungal, antibacterial and steroid ointments. Unrelief of symptoms lead the patient to ask for a specialty evaluation. No specific nor particular aspects were collected in her personal past and recent history; similarily, no recent drug use or abuse was recorded. At inspection, a 3 cm eythematous-white plaque, with exophitic appearance, was present at the upper third of the right labia, involving the clitoris. The margins of the lesion were quite clearly identifiable from the surrounding normal skin and mucosae (Fig. 1). Only a pale reddish aspect around the lesion was identifiable on the external genitalia. No other atypical lesions were present on the entire body surface. Histology of a 6 mm. Keyes' vulvar punch biopsy from the lesion border revealed the presence, within the epidermis, of the typical

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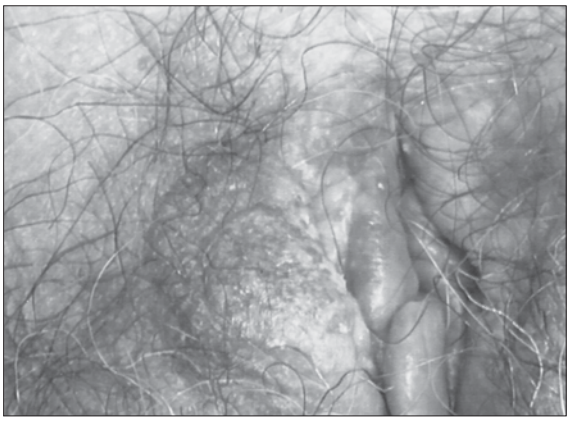

Figure 1. Gross appearance of the vulvar lesion.

pale-staining pagetoid cells arranged in nests and/or forming glands (Figure 2). Immunohistochemistry (Alcian blue, CEA, Keratins and S100 protein) confirmed the diagnosis of Extramammary Paget's Disease (EMPD) of the vulva. The patient was than submitted to multiple biopsies (histological mapping) of the area, excluding invasive foci around the major, clinically evident, lesion. Primitive malignancies from other anatomical sites were excluded with a thorough comprehensive diagnostic workout. Surgical excision with cold blade knife was scheduled and performed under loco-regional anesthesia (spinal block). Surgical specimen confirmed pre-operative diagnosis, with wide free margins (1 cm.). Since then, the patient has been following regular clinical evaluations every three months and she is actually in a clinical complete remission status.

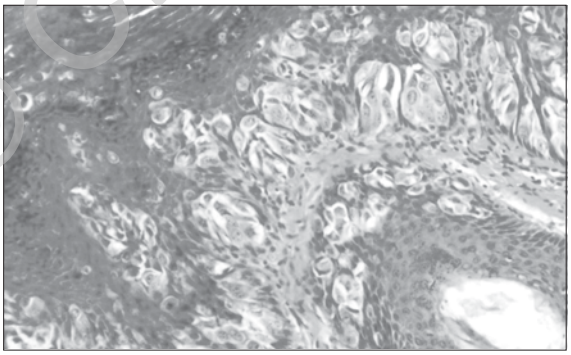

Figure 2. Nest of Pagetoid cells (microphotography).

DISCUSSION

This condition is a rare, of undetermined origin, locally recurrent, chronic proliferative disease, accounting for less than 1% of vulvar neoplasms and lacking of specific signs and symptoms. Because of that, it is frequently misdiagnosed as a candidiasis or dermatitis, determining significative delay in diagnosis. In males, it is almost always localized to the scrotum and/or penis. Lesions are localized in areas with high density of apocrine glands and usually limited to the epithelium, although an invasive subtype is also described. More rarely, Paget's vulvar disease is a superficial expression of a deep adenocarcinoma of cutaneous adnexa or adjacent areas: anorectum, urinary bladder, urethra, Bartholin's gland. The cell origin or Paget's disease of the vulva is still unclear, depending upon various histogenesis theories (1). Different patterns of cells proliferations have been recently described at histology in the in-situ type, demonstrating an interesting correlation with clinical outcome and prognosis (2). Wide surgical excision is the first-line current treatment of choice, independently of the surgical technique adopted (cold knife, CO_2 laser, radiofrequency scalpel); due to the very frequent multifocality of lesions, the disease often extends beyond surgical margins, leading to a high recurrence rate (20-60%). Even in case of free margins, relapses (up to 40%) cannot be excluded in adjacent genital areas (3). Recently a conservative treatment option with imiquimod, mainly in recurrent cases, has been successfully reported both in terms of clinical and pathological remission; dosage and duration of imiquimod cream use are still under evaluation (4). Early and comprehensive diagnosis, conservative surgical approach, intensive follow up and availability of medical options for recurrent disease are the key-points for a successful management of Paget's disease of the vulva.

CONCLUSION

Due to its rarity, Paget's disease of the vulva has a literature that is almost exclusively represented by case reports or very small series. The condition occurs predominantly in postmenopausal women, presenting with

vulvar itching and clinical manifestations of vulvar reddish, erythematous and sometimes excoriated lesions. Long-lasting persistence of symptoms often cause significative diagnosis delay, that, in some circumstances are not only referrable to patients but also to gynecologists' misdiagnosis. For these reasons, vulvar Paget should always be taken into consideration in any differential diagnosis of vulvar affections characterized by pruritus and submitted to histological examination. Complete surgical excision is the treatment of choice; however the disease is well-known to have high rates of involved surgical margins and high rates of local recurrences. In this field, inconsistent results are reported in terms of direct correlation between margin status and recurrence rates. Alternative to repeated surgery approaches in recurrent cases, a medical option based on imiquimod applications has recently been reported with favourable outcomes.

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Inositol supplementation and IVF outcome: preliminary data

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ABSTRACT

Inositol supplementation and IVF outcome: preliminary data.

Myo-Inositol (MI) is involved in several aspects of human reproduction. Elevated concentrations of myo-inositol in human follicular fluids, in fact, seem to play a positive role in follicular maturity, since to represent a possible marker of good oocyte quality.

Nevertheless its positive role in PCOS patients is a consequence of a defect in the insulin signaling (inositol-containing phosphoglycan mediators) pathway that seems to be implicated in the pathogenesis of insulin resistance.

The aim of this study was to analyze the effect of myo-inositol supplementation to "standard" therapy in PCOS women and in "poor responders", submitted to In Vitro Fecundation (IVF) cycles.

In particular, we have investigated its influence on ovarian response to hormonal stimulation and on oocytes quality. Preliminary results of our study, anyway, appear in contrast with results of previous studies; supplementation with MI, in fact, do not seem to improve the response neither in PCOS patients nor in poor responders.

Key words: inositol, ovarian response, oocyte quality, IVF.

SOMMARIO

Supplementazione con inositolo ed esiti della FIV: dati preliminari.

Il mio-inositolo è coinvolto in numerosi aspetti della riproduzione umana. Elevate concentrazioni di mio-inositolo nei fluidi follicolari giocano infatti un ruolo chiave nello sviluppo di ovociti maturi, tanto da fornire un indicatore di buona qualità ovocitaria.

I suoi documentati benefici nel trattamento di pazienti affette da PCOS, inoltre, suggeriscono che un deficit del precursore dell'inositolfosfoglicano, quale appunto è il mio-inositolo, possa rappresentare un cofattore addizionale nella patogenesi dell'insulinoresistenza che caratterizza molte di queste pazienti.

Scopo di questo studio è stato quello di analizzare l'effetto dell'aggiunta di mio-inositolo alla terapia standard in pazienti affette da PCOS ed in pazienti giudicate come "poor responders", sottoposte a cicli di Fecondazione In Vitro (FIV). In particolare, è stata valutata la sua influenza sulla risposta ovarica alla stimolazione ormonale e sulla qualità ovocitaria.

I risultati preliminari del nostro studio dimostrano che la supplementazione con MI non sembra influenzare la risposta alla stimolazione ormonale sia in pazienti con PCOS sia in pazienti "poor responders".

Parole chiave: inositolo, risposta ovarica, qualità ovocitaria, FIV.

INTRODUCTION

Inositol is a sixfold alcohol (polyol) of cyclohexane occurring in nature in the form of nine possible isomers, of which the most widespread is "Myo-Inositol" (MI).

Despite it is classified as a vitaminic factor of B-complex, it's not considered an essential vitamin. In fact, the free rate is greater of that deriving from diet. Main organ of its synthesis is kidney (2g every day for each kidney), that is responsible for its catabolism too. Also brain and testes are two important sites of synthesis.

In nature inositol can be found in free form, or phospholipids-linked, or as phytic acid.

Phospholipids containing inositol (inositides) have an important role in chemical signals transmission systems from outside to inside of cells.

Myo-Inositol is involved in several biological processes: a) transmission of signals mediated by insulin-receptor link; b) cytoskele-

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ton assembly; c) gametogenesis; d) intracellular calcium concentration control; e) membrane potential maintaining; f) gene expression regulation (2).

Inositol and oogenesis

Several evidences emphasize the crucial role of inositol during oocyte maturation.

Chiu et al. showed that increase in intracellular Ca^{++} levels precedes germinal vesicle rupture and oocyte maturation progression. Culture medium supplementation with MI seems able to indirectly promote meiotic maturation (3). On the contrary, inositol depletion in culture media considerably reduces signal transduction mechanisms (2) and alters regulation of Ca^{++} intracellular oscillations (4).

In addition, it seems that follicles with high MI levels contain good quality oocytes.

Presence in follicular fluids of high MI levels, therefore, could be a potential marker not only of a correct follicular development, but also of good oocyte quality (5).

Some studies stress the effects of MI supplementation in patients submitted to IVF cycles who in previous cycles produced poor quality oocytes; in particular, positive effect of MI supplementation is represented by reduction of germinal vesicles and degenerate oocytes number (6,7).

Inositol and PolyCystic Ovarian Syndrome (PCOS)

Women affected by PCOS frequently show an insulinoresistance *pattern* with hyperinsulinemia and glucidic metabolism alterations, till evident pictures of diabetes. In PCOS patients, hyperinsulinemia and insulinoresistance play a direct role in hyperandrogenism pathogenesis, since insulin is able to stimulate internal theca cells to produce high levels of androgens (8).

D-chiro-Inositol (DCI), produced by MI, is an insulin-mediator. A reduced availability or an altered use of DCI or MI could lead therefore to insulinoresistance (9).

Many clinical trials underline the association between insulin tissue sensitivity increment and DCI or MI oral administration for at least 3 months.

DCI shows positive effects on ovulation, in terms of spontaneous recovery, and on androgen production reduction; additionally, contributes to improvement of clinical and metabolic parameters as body weight, arterial pressure and serum triglyceride levels. Similar effects were reported after MI oral administration. These reports suggest that DCI can increase sensitivity to insulin and improve its action in insulinoresistant and in PCOS women (10).

Costantino et al. showed that MI increased sensitivity to insulin, improved tolerance to glucose and reduced insulin relay; additionally, MI caused a reduction in total and free testosterone levels and in total cholesterol levels (11).

Gerli et al. showed, in women PCOS, that MI administered for 16 weeks versus placebo permitted to obtain (12): a) an higher ovulation frequency compared to control group; b) increased E2 levels; c) no change in circulating inhibin or testosterone levels; d) BMI reduction, in contrast with control group; e) circulating LDL and leptin levels reduction; f) no change in circulating androgen concentrations, glycemic indexes, insulinemic values, VLDL levels.

Baillargeon et al. demonstrated a correlation between inositol concentration in serum of patients submitted to IVF cycles and pregnancy rates. It seems that, during embryogenesis, inositol inhibits negative effects of sodium chloride present in culture media. Serum inositol levels before IVF were significantly lower in women who had abortions after IVF, compared to women who had single or multiple ongoing pregnancies.

Papaleo et al. performed on PCOS patients (anovulatory and resistant to 50 mg of CC) a pre-treatment with 4 mg MI and 400 μg folic acid every day for at least 30 days. At the beginning of menstrual flow every patient started intake of 50 mg CC every day for 5 days. Eight patients (66.6%) presented ovulation, four (33.3%) were still resistant to treatment; pregnancies were 3, of which one was multiple. In PCOS treatment, combination of MI with CC 50 mg could be considered the "standard" approach, not only for CC-resistant patients but for all PCOS women, since this

treatment would determine a better control of multiple follicular growth rate and of multiple pregnancy risk.

MI, acting as insulin-sensitizing agent and/or as post-receptor messenger, seems therefore able to restore spontaneous ovarian sensitivity to hormonal stimulation.

Papaleo et al. also investigated the effects of MI administration in 30 patients, treated with ovulation induction stimulation protocols for ICSI. In these patients treatment with MI and folic acid, compared to treatment with folic acid only, reduced the number of degenerate germinal vesicles and degenerate oocytes, without statistically significant differences in the medium number of retrieved oocytes (6).

It's well known, in addition, that PCOS patients treated with multiple follicular growth induction protocols have a significant risk of developing an Ovarian Hyper-Stimulation Syndrome (OHSS) (13). MI could represent in these patients an helpful way to reduce OHSS risk, due to reduction in circulating androgen levels and subsequent reduction in oestradiol levels at human Chorionic Gonadotropin (hCG) administration.

On the basis of literature's results, the aim of our investigation was to study the effects of supplementation with MI to "standard" therapies in two different groups of patients: PCOS and "poor responders" (defined as patients with previous poor responses to high doses of ovulation inductors for ART programs). In particular, our objective was to demonstrate a possible improvement of the response to hormonal stimulation in terms of: 1) presence of response and no cycle cancellation; 2) decreased number of administered r-FSH IU; 3) decreased stimulation lenght; 4) increased retrieved oocytes number.

Additional objectives were: a) in PCOS group, to evaluate if supplementation with MI was associated to a decreased risk for OHSS and subsequent cycle cancellation; b) in poor responders group, to study if MI was able to improve oocyte quality.

MATERIALS AND METHODS

From 2010 January to 2010 September, two groups of patients were recruited: 17 women suffering by PCOS-related chronic anovulation and 12 women classified as "poor responders".

In the first group, PCOS has been diagnosed on the basis of Rotterdam/ASRM criteria, in particular according to the presence of at least two of the following symptoms / signs: a) oligomenorrhea (defined as ≤6 menstrual cycles for year); b) hyperandrogenism signs (hirsutism, acne, alopecia) or hyperandrogenemia (increased total or free T); c) US ovarian morphovolumetry pathognomonic for PCOS. We excluded hypothyroidism cases and other known hyperandrogenism causes. For PCOS group, the inclusion criteria were: 1) age ≤40; 2) infertility duration ≥2 years; 3) documented anovulation (defined by follicular growth US monitoring and associated progesterone assays for at least 3 months); 4) CC-resistance (defined as no response to CC ≥150 mg from day 3 to day 7 of menstrual cycle, for at least three months); 5) negative screening for recurrent pregnancy loss (chromosome mapping, ANA, ENA, APA, thrombophilic screening); 6) no other sensitizing or ovarian stimulating therapy from at least 3 months (metformin, ovulation inductors).

"Poor responder" patients have been classified on the basis of their anamnestic history of poor response in previous stimulation cycles (<3 follicles and oestradiol levels <600 pg/ml at hCG day). In this second group the inclusion criteria were: 1) age ≤40; 2) infertility duration ≥2 years; 3) ≤3 previous ART attempts with documented poor response; 4) negative screening for recurrent pregnancy loss (chromosome mapping, ANA, ENA, APA, thrombophilic screening); 5) no other sensitizing or ovarian stimulating therapy from at least 3 months (metformin, ovulation inductors). Included patients were examinated by a basal US pelvic transvaginal examination at the recruitment day, within day 5 of a spontaneous cycle or a withdrawal bleeding after progestin administration; this basal examination permitted to exclude patients with contraindications to ovulation inductors, such as ovarian cysts.

All the patients of both groups were candidated to ART cycles; for PCOS patients, con-

ventional IVF-ET or ICSI was performed on the basis of male partner semen analysis result, while for all "poor responder" patients the technique was always ICSI, due to the expected low oocyte retrieval and in the attempt to increase oocyte fertilization rate.

Patients were randomized into 4 different treatment groups: 1) PCO-A group: nine PCOS patients who received 2 g MI plus 200 μg folic acid (Inofolic, *Lo.Li Pharma*, Italy) twice a day from at least one month before GnRH-agonist (GnRH-a) administration; 2) PCO-B group: six PCOS patients who received 400 μg folic acid a day; 3) Poor Responders (PR)-A group: eight patients who received 2 g MI plus 200 μg folic acid twice a day from at least one month before GnRH-a administration; 4) PR-B group: six patients who received 400 μg folic acid a day.

In all patients, timing of stimulation was obtained by inducing a withdrawal bleeding with oral EP or progestin administration (Farlutal, *Pharmacia Italia*, Italy; 10 mg once a day for seven days). All PCO women enrolled were down-regulated with a GnRH-a (Decapeptyl 0.1 mg, *Ipsen*, France; 0.05 mg a day) from mid-luteal phase onwards and, when optimally down-regulated, were stimulated with recombinant FSH (r-FSH; Gonal-F, *Merck-Serono*, Switzerland) with a starting dose of 50-150 IU a day. In poor responders GnRH-a was administered according to a "lower doses long protocol": Decapeptyl 0.05 mg a day from mid-luteal phase, reduced to 0.025 mg from day 1 of cycle. Multiple follicular growth induction was performed with r-FSH starting from day 2 of cycle with 300 IU a day, till a maximum dose of 450 mg a day, if the first US monitoring (day 8) revealed no ovarian response. Follicular size was monitored regularly by US and serum estradiol assays. In PCO patients cycle was cancelled in presence of ≥ 20 follicles and if E2 level was ≥2000 pg/ml, in order to avoid OHSS.

On the other hand, in presence of ≤ 2 follicles with a diameter > 16 mm at hCG administration day, cycle was cancelled or converted into Intra Uterine Insemination, on the basis of semen analysis result.

Intramuscolar hCG (Gonasi HP 5000 IU, *Merck Serono*, Switzerland) was administered at a dose of 10,000 IU, and oocyte retrieval was programmed 30 hours later.

As a luteal support, vaginal natural progesterone (Progeffik 200 mg, *Effik Italia*, Italy) was prescribed to all patients on the day of embryo transfer for 14 days; in addition, MI treatment was continued in both A groups patients (MI groups) until serum β-hCG assay.

The statistical significance of the differences between the means was determined and compared by Student's *t*-test. Frequency data were compared using the Fischer exact test. P values <0.05 were taken as statistically significant.

RESULTS

Group A and group B, both for PCOS patients and for "poor responder" patients, resulted homogeneous for those variables that could potentially influence women response to ovulation induction protocols (age, infertility duration, number of previous attempts, primary or secondary infertility, BMI for PCOS) (Tab. 1-2).

Despite the attended results, in PCO-A group (MI) 3 cycles were cancelled due to the high risk of OHSS; it's important to notice that the only case of OHSS, fortunately mild, occurs just in this group. For all the other variables, however, PCOS patients responded similarly both in groups A and B (Tab. 3).

No difference was observed in response to stimulation therapy in group A and B of poor responders; in both these groups, however the total number of administered IV and the number of cancelled cycles remained high while, on the contrary, the oocyte retrieval remained low (Tab. 4).

In PR-A group (MI), of 4 oocytes retrieved in two patients, 3 were of good quality (M II) and originated 2 embryos of good quality too (4 cells grade I and II), while one stopped growing.

In PR-B group, of 4 oocytes retrieved, only one was of good quality (M II), while 2 were germinal vesicles. Of 2 embryos derived from two fertilized oocytes, one stopped growing and the other was of good quality (4 cells grade II) and was therefore transferred.

Table 1 - Main anamnestic and clinical characteristics of Group PCO-A and PCO-B women.

Variables	Group PCO-A (MI) (n=9)	Group PCO-B (n=8)
Age (years)	29.1±4.2 SD	32.3±3.8 SD
Infertility duration (years)	4.6 ±2.2 SD	6.6±4.0 SD
Primary infertility	7 (77.8%)	7 (87.5%)
Patients with previous abortions	2 (22.2%)	1 (12.5%)
Previous attempts	1.0±1.1 SD	2.5±1.7 SD
Total previous attempts	9	20
Amenorrhea	1 (20%)	0
Oligomenorrhea	5 (55.6%)	(87.5%)
BMI ≥25 kg/h^2	4 (44.4%)	4 (50%)
Hyperinsulinemia	3 (33.3%)	4 (50%)

Table 2 - Main anamnestic and clinical characteristics of Group PR-A and PR-B women.

Variables	Group PR-A (MI) (n=6)	Group PR-B (n=6)
Age (years)	36±4.5	34.2±5.4
Infertility duration (years)	4.2±2.4	3.8±2.1
Primary infertility	5 (83.3%)	6 (100%)
Patients with previous abortions	1 (16.7%)	0
Previous IUI / IVF-ET attempts	2.7 1.2	2.3 0.5
Total previous attempts	16	14
Basal FSH > 12 mIU/ml	2 (33.3%)	4 (66.7%)
Previous cancelled cycles	4 (66.7%)	4 (66.7%)

Table 3 - Ovulation induction results in Group PCO-A and PCO-B patients.

	Group PCO-A (MI) (n=9)	Group PCO-B (n=8)
N. cycles with response	9 (100%)	7 (87.5%)
rFSH medium dose (IU)	1712.5+638.6SD	1548+736.7SD
Medium duration of stimulation (days)	11.7±3.9 SD	11.8±3.2 SD
Step-Up/Step-Down Protocol cycles (N.)	1	2
N. cycles with >2 follicles >16mm hCG day	9 (100%)	6 (75%)
N. retrieved oocytes at pick-up	7.5+2.9SD	6.2+4.5SD
N. pregnancies	1 (11.1%)	2 (25%)
N. abortions	0	1
N. cancelled cycles (no hCG) for OHSS risk	3 (33.3%)	1 (12.5%)
N. OHSS	1	0

Table 4 - Ovulation induction results in Group PR-A and PR-B patients.

Variables	Group PR-A (MI) (n=6)	Group PR-B (n=6)
N. cycles with response	5 (83.3%)	5 (83.3%)
rFSH medium dose (IU)	3566.7+1043.9SD	3700+295SD
Medium duration of stimulation (days)	11+2.2SD	11.3+1.0SD
N. cycles with >2 folliles >16mm hCG day	3 (50%)	4 (66.7)
N. retrieved oocytes at pick-up	13	1.25±0.5SD
N. pregnancies	0	0
N. abortions	0	0
N. cancelled cycles (no hCG) for absent response or <2 follicles	3 (50%)	2(33.3%)

DISCUSSION AND CONCLUSIONS

Women affected by PCOS and *"poor responders"* represent two groups of patients extremely different about pathogenetic origin of their infertility, but they have a common poor reproductive prognosis. The epidemiological data are significant: 5-10% of infertile patients are affected by PCOS; "poor responders" are 10-25% of women seen in PMA units (14).

On the basis of these data, the efforts of many research groups working with ART are directed to the improvement of clinical outcome in these patients. The response to exogenous gonadotropin stimulation therapy appears opposite in these two groups: in fact, if this response in poor responders is insufficient, on the contrary in PCOS women is excessive, sometimes abnormal, so much that women affected by PCOS are exposed to a very high risk of OHSS.

Myo-Inositol, according to literature's data, could be one of the factors responsible for oocyte nuclear and cytoplasmic maturation. It is directly correlated to oestradiol levels; an high intrafollicular concentration of MI could represent an oocyte good quality marker, therefore it could be proposed as a possible biochemical marker of oocyte maturity.

Recently its ability to increase tissue sensitivity to insulin and to reduce circulating androgen levels was demonstrated.

We supposed that a possible unrecognized Myo-Inositol deficit could interfere with folliculogenesis and oocyte maturation. We therefore decided to perform a supplementation with MI in PCOS patients and in poor responders, in order to improve the control on follicular growth and recruitment, but also in order to improve oocyte quality, that appears poor in both these groups.

Preliminary results of our study, anyway, appear in contrast with results of previous studies; supplementation with MI, in fact, do not seem to improve the response neither in PCOS patients nor in poor responders. On the contrary, in PCOS-A group (MI) we were obligated to cancel 3 cycles of 9, due to high OHSS risk, while no cycle was cancelled in PCOS-B group.

Moreover, we did not observe advantages in poor responders.

Obviously, the small number of patients included doesn't permit to reach any conclusion, but only to make some preliminary observations. The failure of this therapeutic approach in those patients whose response is poor, could be explained once again with oocyte senescence, on which it is difficult to act, due to the fact that oocytes are cells not subjected to cell renewal.

However, further studies are needed to investigate the effects of supplementation with MI in both the PCOS and the poor responders groups, prolonging the duration of supplementation before the stimulation cycle, but above all by observing its results on a larger number of patients.

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4. **INFORMAZIONI CLINICHE -** 4.1 Indicazioni terapeutiche: In tutti i casi di carenza folica per aumentata richiesta, insufficiente assorbimento, ridotta utilizzazione e insufficiente apporto dietetico della vitamina. 4.2 Posologia e modo di somministrazione: *Soluzione iniettabile*: 1 fiala al giorno secondo prescrizione medica, per via intramuscolare. *Capsule molli*: 1-3 capsule al giorno, s.p.m. Nei bambini la dose giornaliera può essere uguale a quella degli adulti o comunque commisurata, secondo il parere del medico, alle necessità terapeutiche. 4.3 Controindicazioni: Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti. 4.4 Speciali avvertenze e precauzioni per l'uso: Il trattamento va condotto sotto controllo ematologico. In caso di anemia perniciosa, l'acido folico non deve essere somministrato da solo o in associazione con dosi inadeguate di cianocobalamina. Infatti, pur provocando una risposta emopoietica, non svolge alcuna azione preventiva sulla degenerazione midollare subacuta presente in queste forme. Pertanto la somministrazione di acido folico deve essere subordinata ad un preciso accertamento diagnostico ematologico. Da non usarsi come antianemico nei soggetti portatori di neoplasie.
TENERE FUORI DALLA PORTATA DEI BAMBINI.
4.5 Interazioni con altri medicinali e altre forme di interazione: L'acido folico ad alte dosi può ridurre l'effetto antiepilettico del fenobarbital, della fentoina e del primidone. 4.6 Gravidanza e allattamento: L'uso del farmaco non è controindicato in gravidanza e in corso di allattamento. Non vi sono dati di sicurezza per un impiego a dosi superiori a 4-5 mg/die; pertanto in tali situazioni la dose giornaliera non deve superare i 5 mg. 4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari: L'uso del farmaco è compatibile con la guida dell'auto e con l'uso di macchine in genere. 4.8 Effetti indesiderati: Sono stati segnalati rari casi di allergia, anoressia, nausea, tensione addominale, disturbi del sonno, incubi notturni, malessere, irritabilità. 4.9 Sovradosaggio: 15 mg di acido folico al giorno coprono ampiamente il fabbisogno in caso di carenza vitaminica specifica. Non sono descritti in letteratura casi di iperdosaggio.

5. **PROPRIETA' FARMACOLOGICHE -** 5.1 Proprietà farmacodinamiche: Categoria farmacoterapeutica: farmaci antianemici: acido folico e derivati; codice ATC: B03BB01. Effetti farmacodinamici: l'acido folico interviene in numerose reazioni biochimiche come trasportatore di unità monocarboniose in forma attivata. La carenza di acido folico dà luogo ad anemia macrocitica e leucopenia. 5.2 Proprietà farmacocinetiche: L'acido folico per via orale viene in gran parte assorbito come tale e in parte dopo riduzione e metilazione. Penetrando nei tessuti l'acido folico sposta i folati ridotti endocellulari immettendo in circolo 5-CH_3-FH_4. Dopo 180' dalla somministrazione di 5 mg di acido folico per via orale nell'animale e nell'uomo, i livelli sierici di acido folico risultano ancora elevati. La metabolizzazione dell'acido folico è rapportata all'entità dei depositi dei folati aggiustandosi su una omeostasi di saturazione di questi. 5.3 Dati preclinici di sicurezza: Non è stato possibile stabilire la DL_{50} per via orale nell'animale, data la bassissima tossicità dell'acido folico. La vitamina somministrata e.v. è risultata avere una DL_{50} di circa 500 mg/Kg leggermente variabile a seconda della specie animale. Per quanto riguarda la tossicità cronica, dosi inferiori a 50 mg/Kg nel coniglio e nel ratto intraperitoneo non hanno procurato effetti patologici. Le dosi sopracitate sono ampiamente superiori alle usuali dosi terapeutiche nell'uomo. L'acido folico non è tossico per l'uomo anche nella somministrazione ad alta dose e molto prolungata nel tempo come è stato dimostrato in corso di epilessia, somministrando 15 mg al giorno di acido folico per un anno.

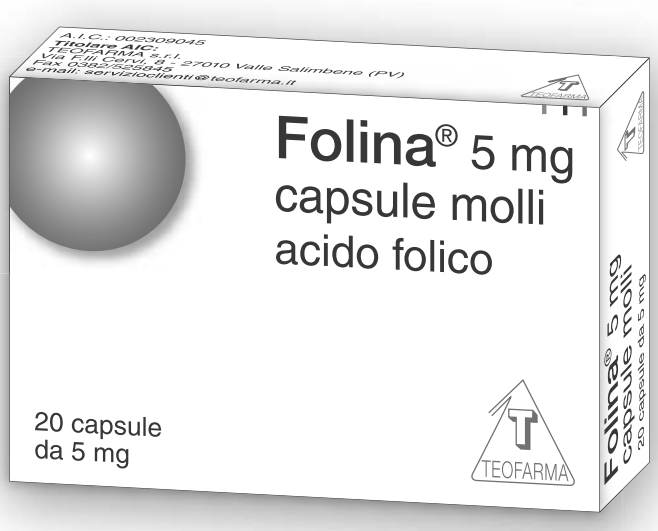
6. **INFORMAZIONI FARMACEUTICHE -** 6.1 Elenco degli eccipienti: Folina fiale: glicina; sodio idrato; sodio cloruro, p-idrossibenzoato di metile, etile, propile, butile, benzile, acqua per preparazioni iniettabili. Folina capsule molli: cera d'api; olio di soia, lecitina di soia in olio di soia. Composizione dell'involucro esterno gelatinoso: gelatina, glicerolo, sodio p-idrossibenzoato di etile, sodio p-idrossibenzoato di propile, sorbitolo, titanio biossido (E 171), eritrosina (E127), ferro ossido nero (E172). 6.2 Incompatibilità: L'azione della Folina è inibita da contemporaneo impiego di farmaci ad azione antifolica. 6.3 Periodo di validità: 3 anni. 6.4 Speciali precauzioni per la conservazione: Conservare in confezionamento integro nelle ordinarie condizioni ambientali. 6.5 Natura e contenuto del contenitore: *Soluzione iniettabile*: fiale in vetro gialli tipo I F.U. Confezione contenente 5 fiale in cassonetto in PVC inserito in astuccio litografato. *Capsule molli*: blisters con alveoli in PVC, sigillati con foglio di alluminio: Confezione contenente 2 blisters da 10 capsule ciascuno inseriti in astuccio litografato. Confezione contenente 6 blisters da 10 capsule ciascuno inseriti in astuccio litografato.E' possibile che non tutte le confezioni siano commercializzate. 6.6 Istruzioni per l'uso e la manipolazione: Nessuna in particolare.

7. **TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO**
Teofarma S.r.l. - Via F.lli Cervi, 8 - 27010 Valle Salimbene (PV)

8. **NUMERO DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO**
Fiale: Cod. N. 002309033
20 capsule: Cod. N. 002309045
60 capsule: Cod. N. 002309058

9. **DATA DI PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE -** 04/08/1982/Giugno 2010

10. **DATA DI REVISIONE DEL TESTO -** Febbraio 2012



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