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Table of contents

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Guidelines for diagnosis and treatment of endometriosis

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TABLE OF CONTENTS

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AUTHORS

These Recommendations have been written by a group of medical professionals (Drafters) identified by SIGO, AOGOI and AGUI Scientific Committees with the organizational support of the Confalonieri-Ragonese Foundation.

RECIPIENTS

These Recommendations are addressed to all professionals who deal with the diagnosis and treatment of the diseases covered by these guidelines.

METHODS

Writing medical Recommendations is a complex activity in terms of methods, and requires advanced technical skills, resources and time that companies usually are not able to provide. These recommendations are based on systematic reviews.

Today, however, acquiring the critical skills required to assess the extent to which systematic reviews (or already existing Guidelines/ recommendations produced in Italy or in other countries) are sufficiently valid from a scientific point of view to be taken into account for their application in Italy is the priority, and not writing new systematic reviews.

Based on these considerations, the production of these Recommendations included the following operational phases:

- Identification of expert drafters
- Identification of systematic reviews and the most recent guidelines published on the topic
- Formulation of clinical themes used to develop the guidelines
- Definition of recommendations by individual drafters through their response to the identified clinical themes
- Definition of the recommendations grading by the group of expert drafters

Specifically, the Quality Level and the strength of these recommendations were graded and expressed in Roman numerals (I to VI) and in letters (A to E). The Quality Level refers to the likelihood that a certain amount of knowledge derives from studies planned and conducted in such a way as to produce valid information without systematic errors, while the Strength of

Recommendation refers to the likelihood that the practical application of a recommendation will lead to an improvement in the health status of the target population to which the recommendation is addressed.
The Level of Quality and Strength of Recommendations were defined according to the criteria suggested by the Methodological Manual of the National Guidelines System (**table 1**).

Table 1.
Quality level and Strength of the Recommendations - Grading. From: ISS-PNLG 2002

	QUALITY LEVEL
I	Evidence obtained from multiple randomised controlled trials and/or systematic reviews of randomised trials
II	Evidence obtained from a single randomised study of adequate design
III	Evidence obtained from non-randomised cohort studies with concurrent or historical controls or their meta-analysis
IV	Evidence obtained from retrospective case-control studies or their meta-analyses
V	Evidence obtained from case studies («case series») without a control group
VI	Evidence based on the opinion of authoritative experts or expert committees as indicated in the guidelines or consensus conferences, or based on the opinions of the members of the working group responsible for these guidelines
	STRENGTH OF THE RECOMMENDATION
A	The execution of that particular procedure or diagnostic test is strongly recommended. It indicates a particular recommendation supported by good quality scientific evidence, even if not necessarily type I or II
B	There are doubts about whether that particular procedure or surgery should always be recommended, but it is believed that its execution should be carefully taken into account
C	There is substantial uncertainty in favour of or against the recommendation to perform the procedure or surgery
D	The execution of the procedure is not recommended
E	The execution of the procedure is strongly discouraged

To develop these phases, an operational meeting was organised during the SIGO-AOGOI AGUI National Congress, followed by an exchange of material and comments via email.
The Recommendations approved by a majority of the Group of Drafters have been revised by the Auditors appointed by the three Scientific Committees.

BACKGROUND

In recent years, several scientific societies have produced consensus guidelines/documents or recommendations for the treatment of endometriosis. In Italy, guidelines were produced for the treatment of pelvic endometriosis in the late '90, using the Delphi' method by the collaborative Group of Italian Endometriosis Study Group (GISE). Many recommendations/ guidelines published are similar to each other and without any special changes over the years, an aspect that indicates the shortage of high-quality and innovative recent studies. However, the therapeutic scenario has in part changed in recent years, also following the introduction of new therapeutic diagnostic methodologies or molecules.
Objective of this document is to provide Italian gynecologists a useful tool in clinical practice, based on updated evidences.

SECTION 1: OVARIAN ENDOMETRIOSIS

1.1 Diagnosis

1.1.1 Role of ultrasound

Transvaginal ultrasound (TV) should be the first diagnostic approach in case of ovarian endometriosis. The diagnostic accuracy of transvaginal ultrasonography for the diagnosis of ovarian endometriosis is very high.

Recommendation	Level of evidence	Strength of recommendation
Transvaginal ultrasound (TV) should be the first diagnostic approach in case of (suspected) ovarian endometriosis	V	A

1.1.2 Diagnostic Criteria

A "typical" endometrioma usually appears at ultrasound as a unilocular or, less frequently multilocular (with a low number of locules) cyst, with a homogeneous low-level echogenicity (ground glass) of the fluid content and regular walls with poor vascularization [1,2].
Some endometriomas can contain scarcely vascularized internal septa or can present as a fluid-dense cysts with an internal hyperechogenic level and a poor pericystic vascular pattern.
Color/power Doppler analysis of endometriotic cysts is useful in the differential diagnosis with other histotypes of adnexal masses [2,3].
Endometriomas with atypical appearance may present hyperechogenic internal content due

to blood clots or fibrin deposits lying adjacent to the cyst wall. Such content will show no vascularisation at Doppler examination.

Ovarian endometriosis is frequently associated with pelvic adhesions and deep infiltrating lesions. The percentage of this association varies from 20 to 80%. When both ovaries present adhesions they may tend to prolapse in the pouch of Douglas and adhere posteriorly to the uterine wall showing the typical so-called "kissing ovaries" ultrasonographic sign, possibly associated with concomitant posterior infiltrating endometriosis (20%) and tubal involvement (90%)[4]. A detailed ultrasonographic evaluation of pelvic adhesions, deep pelvic lesions and adenomyosis is of outmost importance in patients with ovarian endometriosis [5].

The sonographic appearance of endometriomas may vary depending on the hormonal status of the patient. Post-menopausal endometriomas more frequently appear as solid or multilocular-solid cysts with anechoic fluid content or with mixed echogenicity fluid content, sometimes mimicking borderline or malignant neoplasia [6].

The ultrasound pattern of endometriomas may transform also during pregnancy. In pregnant patients the typical endometrioma can undergo a decidualization process and appear as a unilocular- or multilocular-solid cyst, due to the presence of internal papillae, with a regular and smooth surface and often vascularized at Power Doppler examination. In these cases, knowledge of the presence of the endometrioma before pregnancy can facilitate a correct diagnosis and minimize the risk of unnecessary surgery [7].

Borderline and malignant tumors arising from endometriomas are rare (more often endometrial or clear call trimas): in these cases they show typical sonographic features of non-benign adnexal pathology such as cysts with vasularized internal papillar or solid tissue. Patients with an endometrioma that also present associated risk factors (e.s. familiar hystory of malignancy, menopause, infertility, long term persistent cysts) should undergo careful US follow-up with surgical removal and histologic evaluation when suspicious findings arise [8].

Recommendation	Level of evidence	Strength of recommendation
Color/power Doppler evaluation of endometriosis cysts may be useful in the differential diagnosis with other types of adnexal conditions	V	B

1) Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I, **International Ovarian Tumor Analysis G. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group**. Ultrasound Obstet Gynecol 2000; 16: 500–505.

2) Exacoustos C, Manganaro L, Zupi E. **Imaging for the evaluation of endometriosis and adenomyosis**. Best Pract Res Clin Obstet Gynaecol. 2014;28:655-81.

3) Van Holsbeke C, Van Calster B, Guerriero S, Savelli L, Paladini D, Lissi AA, Czekierdowski A, Fischerova D, Zhang J, Mestdagh G et al. **Endometriomas: their ultrasound characteristics**. Ultrasound Obstet Gynecol 2010;35:730–740.

4) Ghezzi F, Raio L, Cromi A, Duwe DG, Beretta P, Buttarelli M, MuellerMD. **"Kissing ovaries": a sonographic sign of moderate to severe endometriosis**. Fertil Steril 2005; 83: 143–147.

5) Exacoustos C, Malzoni M, Di Giovanni A, Lazzeri L, Tosti C, Petraglia F, Zupi E. **Ultrasound mapping system for the surgical management of deep infiltrating endometriosis**. Fertil Steril. 2014;102:143-150.

6) Guerriero S, Van Calster B, Somigliana E, Ajossa S, Froyman W, De Cock B, Coosemans A, Fischerová D, Van Holsbeke C, Alcazar JL, Testa AC, Valentin L, Bourne T, Timmerman D. **Age-related differences in the sonographic characteristics of endometriomas**. Hum Reprod. 2016;31:1723-31.

7) Mascilini F,Moruzzi C, Giansiracusa C, Guastafierro F, Savelli L, De Meis L, Epstein E, Timor-Tritsch IE, Mailath-Pokorny M, Ercoli A, Exacoustos C, Benacerraf BR, Valentin L, Testa AC. **Imaging in gynecological disease. Clinical and ultrasound characteristics of decidualized endometriomas surgically removed during pregnancy**. Ultrasound Obstet Gynecol 2014; 44: 354–60.

8) Nezhat FR, Apostol R, Nezhat C, Pejovic T. **New insights in the pathophysiology of ovarian cancer and implications for screening and prevention**. Am J Obstet Gynecol 2015; 213):262-7.

1.2 Medical Therapy

The objectives of medical therapy in case of ovarian lesion are:

- treatment of the ovarian lesion before or instead of surgery
- reduction of risk recurrence after surgery
- pain control

1.2.1 Medical therapy vs surgery

The treatment of endometrioma depends mainly by the symptoms and the patient's desire of pregnancy. Options include waiting, medical or surgical therapy, and assisted reproduction techniques (ART).

Yap and Collaborators [(1)] in a review of the literature considered the role of medical treatment pre-and post-surgery according to cyst size, pain and infertility. With regard to pre-operative therapy, two studies were included: in both of them there was a difference in the size of the endometrioma of 1-2 cm between the treated vs untreated group, but there was no evidence of a clinical benefit of therapy.

Muzii et al. [(2)], in a recent meta-analysis on the efficacy of combined oral contraceptives (COC), administered cyclically versus non-cyclically, showed no significant reduction in endometrioma before surgical treatment on post-operative outcome. The efficacy of progestins in ovarian endometriosis has been object of several studies [(3-5)]. A randomized multicenter study evaluated the efficacy of administration of dienogest in 187 women, with a statistically significant reduction in the size of the cysts [(5)]. In consideration of side effects, therapy with GnRH agonists or with danazol (equally effective) should be considered as second-line treatment [(6-9)]. Medical therapy is symptomatic and not cytoreductive [(10, 11)].

Recommendation	Level of evidence	Strength of recommendation
Medical treatment of ovarian endometriosis (endometrioma) can be considered in case of lesions of limited size, but we have no data that allow us to consider such treatment as effective in the long period	V	B
Medical treatment with progestins alone (IA) or with estrogens (IIIA) may be considered in patients with pain and waiting for surgery with the goal of controlling pain but not of improve surgical outcomes	I	A

1) Yap C, Furness S, Farquhar. **Pre and post-operative medical therapy for endometriosis surgery**. Cochrane Database Syst Rev. 2004:CD003678.

2) Muzii L, Di Tucci C, Achilli C, Di Donato V, Musella A, Palaia I, Panici PB. **Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and metaanalysis**. Am J Obstet Gynecol. 2016 Feb;214(2):203-11

3) Andres Mde P1, Lopes LA, Baracat EC, Podgaec S. **Dienogest in the treatment of endometriosis: systematic review**. Arch Gynecol Obstet. 2015 Sep;292(3):523-9.

4) Kohler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO (2010). **A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of dienogest daily for endometriosis**. Int J Gynaecol Obstet 108(1):21–25

5) Momoeda M, Taketani Y. **A randomized, double-blind, multicenter, parallel, dose-response study of dienogest in patients with endometriosis**. Jpn Pharmacol Ther 2007;35:769-83

6) Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Crosignani PG. **Endometriosis: current therapies and new pharmacological developments**. Drugs 2009;69:649–75

7) Crosignani PG, Luciano A, Ray A, Bergqvist A. **Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain**. Human Reprod 2006;21:248–56.

8) Surrey ES. **Gonadotropin-releasing hormone agonist and add-back therapy: what do the data show?** Curr Opin Obstet Gynecol 2010;22:283–8.

9) Somigliana E, Vigano P, Barbara G, Vercellini P. **Treatment of endometriosis related pain: options and outcomes**. Front Biosci 2009;1:455–65

10) Vercellini P, Viganò P, Somigliana E, Fedele L. **Endometriosis: pathogenesis and treatment**. Nat. Rev. Endocrinol 2014 May;10(5):261-75

11) Johnson N. P., Hummelshoj L. **World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis**. Hum. Reprod. 28, 1552-1568 (2013)

1.2.2 Medical therapy to lower the risk of recurrence of ovarian lesion after surgery

The risk of recurrence of the ovarian lesion after surgery is about 10% per year for the first five years [(1)]. In consideration of the impact of surgery on the ovarian function, it is necessary to improve clinical strategies aimed to prevent repeated surgery, especially in young and not searching pregnancy patients [(2,3)].

Medical therapy after surgery for endometriosis has the objective of reducing the risk of long-term relapses, defined as recurrence of symptomatology or lesion after 12/24 months after surgery.

There is some evidence that post-surgical combined oral contraceptive (COC) use lower the risk of recurrences of ovarian endometriosis.

In a randomized controlled prospective study women who underwent laparoscopic enucleation of endometrioma were allocated to: no treatment, treatment with low doses monophasic COC for 24 months in cyclic or continuous regimen.

The 2-year recurrence rate was significantly lower in treated patients (cyclic regimen: 14.7%, continuing regimen: 8.2%, no treatment 29%). In cases of recurrence in treated patients with both regimens of administration, size and growth of the lesions were significantly lower than among the untreated patients. There were no significant differences between the continuous and cyclic regimes [4].

The similar efficacy of cyclic and continuous regimen in the prevention of recurrence of ovarian endometriosis is confirmed by another randomized prospective study, which reports, however, more side effects among patients treated with continuous regimen [5].

A controlled randomized study has analyzed the COC's efficacy in the prevention of relapses with different progestin formulation. The three regimens tested with different progestins (desogestrel, gestodene and dienogest), showed no significant difference (26.5%, 31.8%, 20.5%). The recurrence rate of untreated patients (74.7%) was significantly higher than in any COC treatment group [6]. Ota et al. [7] showed in a retrospective cohort study that the recurrence rate is significantly lower in patients with ovarian endometriosis treated with dienogest for five years after surgery, than in untreated patients (69% vs. 4%; OR = 0.09; 95% CI = 0.03 – 0.26; P < 0.0001) In this study anemia occurred in 4% due to metrorrhagia directly after administration, metrorrhagia including spotting was observed in 20% at 1 year and decreases in bone mineral density and depression were observed in 4 and 2.6%, respectively, in the dienogest group: these conditions did not require treatment interruptions.

Recommendation	Level of evidence	Strength of recommendation
After cystectomy for endometrioma, hormonal therapy with progestins alone is recommended	I	A
The choice of post-surgical treatment should be based on fertility desires, patient's preferences, costs and safety profile	VI	B
There is no difference in terms of recurrence rates among the different estroprogestins	II	A

1) Guo, S.W. **Recurrence of endometriosis and its control**. Hum Reprod Update. 2009; 15: 441–461

2) Busacca, M., Riparini, J., Somigliana, E. et al. **Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas**. Am. J. Obstet. Gynaecol. 2006; 195: 421–425

3) Vercellini, P., Somigliana, E., Viganò, P., de Matteis, S., Barbara, G., and Fedele, L. **The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review**. Acta Obstet Gynecol Scand. 2009; 88: 1074–1082

4) Seracchioli R, Mabrouk M, Frascà C, Manuzzi L, Montanari G, Keramyda A, Venturoli S. **Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial**. Fertil Steril 2010 Jan;93(1):52-6

5) Muzii L., Di Tucci C., Achilli C., Di Donato V., Musella A., Palaia I., Panici P.B. **Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and metaanalysis**. Am J Obstet Gynecol. 2016; 214(2):203-11

6) Cucinella, G., Granese, R., Calagna, G., Svelato, A., Saitta, S., Tonni, G. et al. **Oral contraceptives in the prevention of endometrioma recurrence: does the different progestins used make a difference?**. Arch Gynecol Obstet. 2013; 288: 821–827

7) Ota, Y., Andou, M., Yanai, S., Nakajima, S., Fukuda, M., Takano, M. et al. **Long-term administration of dienogest reduces recurrence after excision of endometrioma**. J Endomet Pelv Pain Disord. 2015; 7: 63–67

1.2.3 Medical therapy in the control of pain

In case of pain, medical therapy of patients with ovarian endometriosis is similar to that of patients with superficial or deep endometriosis.

In presence of pain symptomatology, progestins alone or, in particular in case of contraceptive needs, in association with estrogen, should be considered as first choice treatment [1].

Controlled randomized studies have compared the use of GnRH agonists vs progestins alone or COC in the treatment of pain associated with endometriosis: a higher frequency of side effects in the GnRH group was reported.

Regidor et al. [2] compared Linestrenolo with Leuprorelina: In the Linestrenolo group there was a reduction of dysmenorrhoea in 50% of patients and chronic pelvic pain in 59% of cases after 6 months of treatment, vs 85 and 69%. In the Leuprorelina group respectively.

Strowitzki et al. [3] compared the use of dienogest vs monthly Leuprorelina and showed a similar reduction in pain symptomatology in the two groups and greater tolerability of the Dienogest.

Guzick et al. [4] compared a COC-based ethinyl estradiol-norestisterone (35 mg/1 mg per day) vs Leuprorelina 11.25 mg every 2 weeks and norestisterone 5 mg day). In both groups a

reduction in pain was observed.
Systematic reviews of controlled randomized trials [5,6] concluded that GnRH treatments, COC and progestins are equally effective in the control of pain associated with endometriosis. Studies have shown that dienogest (2 mg/day) is an effective (in comparison with placebo) therapy for the control of pain in patients with endometriosis. Desonorgestrel has shown similar results as GnRH analogues in pelvic pain control and in all other endometriosis-related symptoms. There are no studies comparing desonorgestrel with other progestin or oestrogens formulations as a first-line therapy in the control of pain symptomatology associated with endometriosis.

Recommendation	Level of evidence	Strength of recommendation
Progenstins alone or COC are the most efficaciuous treatments	III	A

1) Vercellini P., Buggio L., Berlanda N., Barbara G., Somigliana E., Bosari S. **Estrogen-progestins and progestins for the management of endometriosis**. Fertil Steril 2016 Dec; 106 (7):1552-1571.
2) Regidor PA., Regidor M., Schmidt M., et al. **Prospective randomized study comparing the GnRH-agonist leuprorelin acetate and the gestagen lynestrenol in the treatment of severe endometriosis**. Gynecol Endocrinol 2001;15:202-9.
3) Strowitzki T., Marr J., Gerlinger C. et al. **Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis; a 24-week, randomized, multicentre, open-label trial**. Hum Reprod 2010;25:633-41.
4) Guzick DS., Huang LS., Broadman BA., et al. **Randomized trial of leuprolide versus continuous oral contraceptive in the treatment of endometriosis-associated pelvic pain**. Fertil Steril 2011;95:1568-73.
5) Jeng CJ., Chuang L., Shen J. **A comparison of progestogens or oral contraceptives and gonadotropin-releasing hormone agonists for the treatment of endometriosis: a systematic review**. Expert Opinion on Pharmacotherapy, 2014; 15: 767-73.
6) Andres M., Lopes L., Baracat E., Podgaec S. **Dienogest in the treatment of endometriosis: systematic review**. Arch Gynecol Obstet 2015. 292:523-529.

1.2.4 Medical therapy in adolescents
Lacking specific data guidelines for adult women should be considered.
COC (cyclic or continuous use) associated with non-steroidal anti-inflammatory drugs are indicated as first line treatment.
If the first-line therapies do not work, taking into account age and side effects, all the therapies available for endometriosis in adults can be used in adolescents as second-line therapies.
Clinicians should use GnRH-agonists cautiously, since teenagers may not have reached the maximum bone density [1].

Recommendation	Level of evidence	Strength of recommendation
In adolescents, the treatment of choice are COCs	VI	B

1) Lee DY, Kim HJ, Yoon BK, Choi D. **Clinical characteristics of adolescent endometrioma**. J Pediatr Adolesc Gynecol. 2013 Apr;26(2):117-9.

1.3 Surgical Therapy
1.3.1 Role of surgical therapy in the treatment of endometrioma
Surgical treatment of endometrioma is indicated if symptoms are or become not responder to medical therapy, or the endometrioma increases in volume or is greater than 3 cm in diameter in infertile patients [1,2].

Recommendation	Level of evidence	Strength of recommendation
Surgery should be considered in symptomatic women Or if endometrioma increases in volume or is greater than 3 cm in diameter in infertile patients	VI	B

1) Practice Committee of the American Society for Reproductive Medicine. **Treatment of pelvic pain associated with endometriosis: a committee opinion**. Fertil Steril. 2014 Apr;101(4):927-35. Erratum in: Fertil Steril. 2015; 104(2): 498.
2) Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W. **European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis**. Hum Reprod. 2014; 29(3): 400-12.

1.3.2 Surgical modalities in the treatment of endometrioma.
Laparoscopy is the gold standard for the treatment

of endometriosis, due to faster recovery, better post-operative outcome and reduced hospital costs. Ovarian cystectomy compared to laser vaporization or coagulation of the cystic bed, lowers the number of recurrences and is associated with an increase rate of spontaneous pregnancies in the short and long term [1-3].

Laser vaporization techniques are currently under evaluation in clinical studies with the aim of making the procedure reproducible and safe for the ovarian tissue.−A further application of the CO2 Laser involves the combined use of the excisional and the ablative surgery: a large part of the cystic capsule of the endometrioma is stripped followed by vaporization of the remaining part of the capsule. The combined technique respects the vascularization of the ovarian parenchyma, guarantees a greater preservation of the volume and the follicular count, compared to cystectomy. In addition, an increase in the rate of spontaneous pregnancies and a reduction in recurrences [4] have been reported.

The damage of ovarian parenchyma is inversely related to the experience of the surgeon [5].

Surgically treated patients showed an increase of 50% of spontaneous pregnancy 1-2 years after surgery [6,7]. However, it has been shown that the rate of spontaneous ovulation [8-10], as well as the response to ovarian hyperstimulation, are lowered after surgery [11].

Recommendation	Level of evidence	Strength of recommendation
Ovarian cystectomy when compared to laser vaporization or coagulation of the cystic bed, lowers the number of recurrences	II	A

1) Carmona F, Mart_ınez-Zamora MA, Rabanal A, Martinez-Rom_an S, Balasch J. **Ovarian cystectomy versus laser vaporization in the treatment of ovarian endometriomas: a randomized clinical trial with a five-year follow-up**. Fertil Steril. 2011; 96: 251–254

2) Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. **Management of ovarian endometriomas**. Hum Reprod Update. 2002 ; 8(6): 591-7.

3) Hart, R. J., Hickey, M., Maouris, P. & Buckett, W. **Excisional surgery versus ablative surgery for ovarian endometriomata**. Cochrane Database of Systematic Reviews, Issue 2; 2008: Art. No.: CD004992.

4) Donnez J, Wyns C, Nisolle M. **Does ovarian surgery for endometriomas impair the ovarian response to gonadotropin?** Fertil Steril. 2001; 76: 662–665.

5) Muzii L, Marana R, Angioli R, et al. **Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter?** Fertil Steril. 2011; 95: 2116–2119.

6) De Ziegler D, Borghese B, Chapron C. **Endometriosis and infertility: pathophysiology and management**. Lancet. 2010; 376: 730–738.

7) Adamson DG. **Laparoscopy, in vitro fertilization, and endometriosis: an enigma**. Fertil Steril. 2005; 84: 1582–1584.

8) Leone Roberti Maggiore U, Scala C, Tafi E, Racca A, Biscaldi E, Vellone VG, Venturini PL, Ferrero S. **Spontaneous fertility after expectant or surgical management of rectovaginal endometriosis in women with or without ovarian endometrioma: a retrospective analysis**. Fertil Steril. 2017 Apr;107(4):969-976.e5. doi: 10.1016/j.fertnstert.2017.02.106.

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10) Horikawa T, Nakagawa K, Ohgi S, Kojima R, Nakashima A, ItoM, Takahashi Y, Saito H. **The frequency of ovulation from the affected ovary decreases following laparoscopic cystectomy in infertile women with unilateral endometrioma during a natural cycle**. J Assist Reprod Genet. 2008; 25: 239–244.

11) Somigliana E, Benaglia L, Paffoni A, Busnelli A, Vigano P, Vercellini P. **Risks of conservative management in women with ovarian endometriomas undergoing IVF**. Hum ReprodUpdate. 2015; 21(4): 486-99.

1.3.3 Effect of surgery on ovarian reserve

Recent studies have shown that the laparoscopic stripping technique is associated with a reduction of the ovarian reserve, as documented by a reduction in the levels of postoperative Antimullerian hormone (AMH) [1]. Otherwise it has been suggested that AMH is lowered independently by the type of surgical procedure used [2]. The clinical consequences of surgical impairment are limited in cases of unilateral endometrioma [3,4]. On the contrary, the damage can become clinically relevant in cases of bilateral endometriomas. in this case a higher frequency of premature ovarian failure has been observed. Surgical treatment is not recommended in teens and young women who are searching pregnancy and are asymptomatic. In view of the reduction of the ovarian reserve and the increased risk of premature ovarian failure, especially in patients with bilateral endometrium, several

cryopreservation techniques are currently available [5].

Recommendation	Level of evidence	Strength of recommendation
No evidences are available on the comparative effect of different surgical techniques on ovarian reserve after surgery	V	A

1) Raffi F, Metwally M, Amer S. **The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis**. J Clin Endocrinol Metab. 2012; 97(9): 3146–54.
2) Saito N, Okuda K, Yuguchi H, et al. **Compared with cystectomy, is ovarian vaporization of endometriotic cysts truly more effective in maintaining ovarian reserve?** J Minim Invasive Gynecol. 2014; 21(5): 804–10.
3) Demirol A, Guven S, Baykal C, Gurgan T. **Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study**. Reprod Biomed Online. 2006; 12: 639–643.
4) Tsoumpou I, Kyrgiou M, Gelbaya TA, Nardo LG. **The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis**. Fertil Steril. 2009; 92: 75–87.
5) Donnez J, Dolmans MM. **Cryopreservation and transplantation of ovarian tissue**. Clin Obstet Gynecol. 2010; 53(4): 787-96.

1.4 Approach to the infertile patient

1.4.1 Endometrioma as cause of infertility

Endometrioma may be a cause of infertility. The impact of endometrioma and its surgical treatment have been the subject of a recent meta analysis including 30 retrospectives and 3 randomized studies [1].

Women with endometrioma admitted to IVF/ICSI have shown a clinical outcome similar to that observed in women whithout endometrioma, but showed a lower mean number of oocyte retrieved.

Recommendation	Level of evidence	Strenght of recommendation
Endometriosis should be always considered in the diagnostic work up of infertility	III	A

1) Hamdan M, Dunselman G, Li TC, Cheong Y. **The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis**. Human Reproduction Update, 2015; 21,6: 809–825.

1.4.2 Surgical treatment before ART

According to the guidelines of the European Society of Human Reproduction and Embryology[1], the surgical treatment of endometrium > 3 cm in diameter improves fertility better than simple drainage or only coagulation of the cyst.

The conservative treatment of the pseudo-capsule may be associated with a substantial risk of recurrence [1]. Endometriosis is a recurrent disease, thus he timing of management of the infertile patient should take into account future pregnancies. It is necessary to personalize each treatment taking into account other woman's characteristics such as age. Moreover, the presence of endometrioma during the IVF/ICSI treatment may be associated with difficulties in the recovery of the oocytes, contamination of the follicular fluid, potential progression of disease, complications in case of pregnancy. Nevertheless, the presence of endometrioma does not represent a contraindication to IVF/ICSI treatment

Recommendation	Level of evidence	Strenght of recommendation
Surgical treatment should take into account woman's characteristics such as age	VI	C
The presence of endometrioma does not represent a contraindication to IVF/ICSI treatment	VI	C

1) Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W. **European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis**. Hum Reprod. 2014 Mar;29(3):400-12

SECTION 2: PERITONEAL ENDOMETRIOSIS

2.1 Diagnosis

2.1.1 Role of ultrasound and other imaging techniques

Ultrasound is recognized as the most common diagnostic approach and first line imaging technique also for the evaluation of peritoneal endometriosis. MRI is useful when performed by expert operators and should be requested in specific cases that may benefit from further diagnostic investigations, considering it is

burdened by high costs.

Recommendation	Level of evidence	Strength of recommendation
Ultrasound examination should be the first line diagnostic technique in the diagnosis of peritoneal endometriosis	V	A

2.1.2 Sonographic Diagnostic Criteria for peritoneal/ superficial endometriosis

The presence of peritoneal/superficial endometriotic disease with associated adhesions should always be evaluated in patients with complaints of cyclic/chronic pelvic pain.

The US "sliding sign" allows to identify with high accuracy the obliteration of the Douglas pouch due to severe posterior adherences [1], that in turn can be associated with the presence of deep infiltrating endometriosis of the posterior compartment.

This simple maneuver can easily be performed by operators with different levels of expertise and should be routinely carried out when scanning patients with symptoms and a clinical history possibly related to pelvic endometriosis. Moreover, pain complained by patients during ultrasonographic examination in specific anatomic sites can guide in the detection of deep infiltrating lesions.

2.1.3 Sonographic Diagnostic Criteria for tubal endometriosis

Endometriotic tubal involvement is usually superficial, resulting in adhesions that can cause anatomic distortion, functional impairment and ectasia of the tubes.

When tubal occlusion occurs typical sonographic signs of hydrosalpinx can be observed: a tubular unilocular mass with thickened walls, incomplete septa and a fluid anechoic content or a dense content (ground glass) similar to endometrioma (haemato-salpinx).

2.1.4 Ultrasound evaluation in case of pelvic endometriosis infiltrating

Sonographic criteria for the diagnosis and mapping of deep pelvic endometriotic lesions were recently published by a consensus of experts [2]. A correct diagnosis is crucial for adequate clinical and/or surgical management of patients. Diagnostic accuracy of ultrasound performed by expert operators varies from 70 to 90% depending on the specific anatomic location [2,3]. An accurate evaluation of the extension of deep pelvic endometriosis is based on the identification, description and measurement of infiltrating lesions in the anterior, lateral and posterior compartments [4,5].

The typical sonographic features of postero-lateral deep infiltrating endometriotic lesions are the following: solid hypoechoic tissue with irregular margins and poor or no vascularization which alters the normal sonographic appearance of the involved anatomical site. Bladder and vaginal nodules can show a slight increase of the vascularisation when compared to typical postero-lateral lesions [2,5].–For deep infiltrating nodules of the anterior, lateral and posterior paracervical areas it is of outmost importance to verify the extension of the lesion and its distance from the intra-pelvic distal tract of the ipsilateral ureter in order to evaluate urinary tract involvement. In case of doubt or difficult ureteral direct visualization, evaluation of pyelectasis can be easily obtained with trans-abdominal ultrasound in order to identify patients requiring urgent surgical approach [5].

The sonographic evaluation of deep pelvic endometriosis requires specific skills and a high level of expertise arising from adequate training and strict cooperation with pelvic surgeons, which are usually achieved in dedicated tertiary centers.

In order to reduce potential diagnostic delay, even less experienced operator should be able to at least suspect pelvic endometriosis and identify the presence of infiltrating lesions, eventually referring affected patients to dedicated sonographic or MRI operators for further and more accurate investigation.

Recommendation	Level of evidence	Strength of recommendation
Accurate evaluation of deep pelvic endometriosis includes the identification and description of infiltrating lesions in the anterior, lateral and posterior pelvic compartment	V	B
Some easy and feasible maneuvers (sliding sign) allow less experienced operators to identify patients at risk of deep endometriosis that should be referred to dedicated sonographic or MRI operators for further and more accurate evaluation of the pelvic extension of the disease	V	B

1) Reid S, Lu C, Casikar I, Reid G, Abbott J, Cario G, Chou D, Kowalski D, Cooper M, Condous G. **Prediction of pouch of Douglas obliteration in**

women with suspected endometriosis using a new real-time dynamic transvaginal ultrasound technique: the sliding sign. Ultrasound Obstet Gynecol. 2013;41:685-91.
2) Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FP, Van Schoubroeck D, Exacoustos C, Installé AJ, Martins WP, Abrao MS, Hudelist G, Bazot M, Alcazar JL, Gonçalves MO, Pascual MA, Ajossa S, Savelli L, Dunham R, Reid S, Menakaya U, Bourne T, Ferrero S, Leon M, Bignardi T, Holland T, Jurkovic D, Benacerraf B, Osuga Y, Somigliana E, Timmerman D. **Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group**. Ultrasound Obstet Gynecol. 2016;48:318-32.
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4) Exacoustos C, Manganaro L, Zupi E. **Imaging for the evaluation of endometriosis and adenomyosis**. Best Pract Res Clin Obstet Gynaecol. 2014;28:655-81.
5) Exacoustos C, Malzoni M, Di Giovanni A, Lazzeri L, Tosti C, Petraglia F, Zupi E. **Ultrasound mapping system for the surgical management of deep infiltrating endometriosis**. Fertil Steril. 2014;102:143-150.
6) Di Giovanni A, Casarella L, Coppola M, Iuzzolino D, Rasile M, Malzoni M. **Combined transvaginal/ transabdominal pelvic ultrasonographic accurately predict the 3 dimensions of deep infiltrating bowel endometriosis measured after surgery: a prospective study in specialized center**. J Mimim Invasive Gynecol 2018:18 30155-9

2.2 Medical Therapy

2.2.1 Medical therapy in the prevention and therapy of pain syndrome.

Medical treatment has a role in controlling pain and avoiding the progression of injuries. Studies have shown that medical therapies are effective only during their use and the symptoms often recur after the stop of treatment [1].

In women with rectal-vaginal endometriosis, a review of the literature has shown that the effect of medical treatment in terms of pain reduction is substantial [2]. In the presence of pain symptomatology, the use of paracetamol, NSAIDs may be associated to hormonal treatments [3,4].

Recommendation	Level of evidence	Strength of recommendation
Medical therapies are effective only during their use and the symptoms often recur after the stop of treatment	I	A
Progestins alone are the most effective therapy in the reduction of dysmenorrhea, dyspareunia, dischizia and chronic pelvic pain	I	A
Estroprogestestinal treatments are effective in the treatment of dysmenorrhea, but not of chronic pelvic pain	I	A
In the presence of pain symptomatology, the use of paracetamol, NSAIDs may be associated to hormonal treatments	VI	B

1) Vercellini P, et al. **Estrogen-progestins and progestins for the management of endometriosis**. Fertility and Sterility. 2016;106(7):0015-0282.
2) Vercellini P, et al. **Medical Treatment for Rectovaginal Endometriosis: What is the Evidence?** Hum Reprod. 2009;24(10):2504-14.
3) Johonson NP, et al. **Consensus on current management of endometriosis. Human Reproduction**. 2013; 28,6: 1552–15681
4) Brown J, Crawford TJ, Datta S, Prentice A. **Oral contraceptives for pain associated with endometriosis**. Cochrane Database Syst Rev. 2018 May

2.3 Surgical Therapy

2.3.1 The aims of surgical treatment

A conservative approach aimed at restoring normal anatomical conditions with preservation of visceral innervation (nerve sparing techniques) must be the basis of the surgical strategy. Due to the high diagnostic accuracy of imaging techniques, the role of laparoscopy for purely diagnostic purposes is at present extremely limited [1] and histological evidence is not currently needed for treatments planning. The surgical approach should be whenever possible conservative and modulated according to patient's age and desire of pregnancy. Non-conservative surgical treatment should be considered only in cases of pain refractory to any medical and surgical treatment in perimenopausal patients whit no childbearing desire. When surgery is the treatment of choice, it should be appropriately planned and performed by expert operators in order to avoid unnecessary and potentially damaging repeated procedures.

Indications to surgical treatment for pelvic endometriosis are:

- symptomatic superficial/or infiltrating lesions in patient not responsive or with controindications to hormonal medical therapy (symptoms and/or disease progression).

- functional organ damage (bowel subocclusion/occlusion, urinary tract impairment with renal function compromission).

There is no reliable data showing superiority of excision compared to the ablation of lesions in the surgical treatment of peritoneal endometriosis [2]. However, the excisional technique allows histological diagnosis and removal of deep lesions which, to a simple inspection, could erroneously appear as superficial. For these reasons, it is considered that surgical excision of the endometriosis should be chosen when possible [3]. A "patient-centered" approach should represent the cornerstone in the management of patients with endometriosis disease.

Recommendation	Level of evidence	Strenght of recommendation
A conservative approach and nerve sparing must be the basis of the surgical strategy	III	B
Repeated surgeries should be avoided	III	B
Excisional tecnique should be preferred	III	B
Adequate counselling about therapeutic surgical options should be always offered to the patient	VI	B

1) Singh SS, Suen MW. **Surgery for endometriosis: beyond medical therapies**. Fertil Steril. 2017 Mar;107(3):549-554. doi: 10.1016/j.fertnstert.2017.01.001. Epub 2017 Feb 8.

2) Duffy J.M., Arambage K., Correa F.J., Olive D., Farquhar C., Garry R. et al. **Laparoscopic surgery for endometriosis**. Cochrane Database Syst Rev. 2014;:CD011031.

3) Yeung P Jr. **The laparoscopic management of endometriosis in patients with pelvic pain**. Obstet Gynecol Clin North Am. 2014 Sep;41(3):371-83. doi: 10.1016/j.ogc.2014.05.002. Epub 2014 Jul 9. Review.

2.3.2 Surgical technique

Several findings[1] show the superiority of laparoscopy vs laparotomy in the treatment of pelvic endometriosis, provided that the surgical procedure is performed in highly specialized centers for endoscopic pelvic surgery by operators with high level of experience in the treatment of endometriosis ("High volume surgeons").

Preferably procedures should be carried out by surgeons with proven experience in the laparoscopic treatment of extragenital conditions, such as urological or colorectal surgical procedures ("pelvic surgeon").

Otherwise the treatment can be carried out by a multidisciplinary team (gynecologist, general surgeon, urologist), but in any case with proven experience in the treatment of severe pelvic endometriosis.

Recommendation	Level of evidence	Strenght of recommendation
Laparoscopy is the gold standard in the surgical treatment of peritoneal endometriosis	VI	B

1) Jacobson TZ, Duffy JM, Barlow D, Koninckx PR and Garry R. **Laparoscopic surgery for pelvic pain associated with endometriosis**. Cochrane Database Syst Rev 2009:CD001300.

2.4 Approach to the infertile patient

2.4.1 Superficial and deep endometriosis as a cause of infertility

Deep endometriosis has a marked influence on the outcome of ART [1]. Clinical pregnancy rate (CPR) is reduced, being also related mainly to patient's age, serum value of AMH and presence of adenomyosis [2].

A complete evaluation of the couple should always be offered, taking into account not only endometriosis as a cause of infertility, but also of possible concomitant pathologies (e.g. male infertility).

Recommendation	Level of evidence	Strength of recommendation
A complete evaluation of the couple should always be offered, taking into account not only endometriosis as a cause of infertility, but also of possible concomitant pathologies (e.g. male infertility)	III	A

1) Hamdan M, Dunselman G, Li TC, Cheong Y. **Influence of Endometriosis on Assisted Reproductive Technology Outcomes. A Systematic Review and Meta-analysis**. Obstet Gynecol. 2015; 125:79–88.

2) Ballester M, Oppenheimer A, Mathieu d'Argent E, Touboul C, Antoine JM, Nisolle M, Daraï E. **Deep infiltrating endometriosis is a determinant factor of cumulative pregnancy rate after intracytoplasmic sperm injection/in vitro fertilization cycles in patients with endometriomas**. Fertil Steril. 2012 Feb;97(2):367-72.

2.4.2 Surgical treatment before ART

The impact of surgery for deep endometriosis on fertility is controversial. There is no level I evidence regarding the effect of surgery on fertility, thus there is no indication to surgical treatment to improve fertility [1]. In case of surgery, if spontaneous conception does not occur after 6 months, a IVF/ICSI should be recommended.

There is still no clear scientific evidence of the association between miscarriage rate and deep endometriosis [2].

Recommendation	Level of evidence	Strength of recommendation
There is no indication to surgical treatment to improve fertility	VI	B
In case of surgery, if spontaneous conception does not occur after 6 months, a IVF/ICSI should be recommended	IV	B

1) Barbosa MAP, et al. **Impact of endometriosis and its staging on assisted reproduction outcome: systematic review and meta-analysis**. Ultrasound Obstet Gynecol 2014; 44: 261–278.
2) Jacobson TZ, Duffy JM, Barlow D, Farquhar C, Koninckx PR, Olive D. **Laparoscopic surgery for subfertility associated with endometriosis**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001398.

SECTION 3: ENDOMETRIOSIS IN ATYPICAL SITES

3.1 Endometriosis of the abdominal wall, inguinal canal, umbilicus

Endometriosis in these locations can be viewed with high frequency linear probes. Endometriosis appears as hypoechoic areas that interrupt the normal sonographic contour of the tissues.
These hypoechoic nodules have irregular margins and poor vascularity and are painful to palpation especially during menses.
At the umbilical level, endometriosis may show cystic appearance with fluid dense content.

3.2 Endometriosis in other sites

The presence of endometriosis in other sites should be suspected on a clinical basis.
Ultrasound examination is often not useful in case of deep abdominal (diaphragm) lesions and is non-diagnostic for thoracic and cranial lesions.
The ultrasound examination does not appear to be diagnostic in case of endometriosis involving nervous structures.

Recommendation	Level of evidence	Strength of recommendation
Contrast enhanced ultrasound techniques to MRI and other imaging tecnhinques should be considered in the diagnosis of endometriosis of atypical sites	V	B

3.2.1 Bowel deep endometriosis

The infiltrating endometriosis nodule appears as a hypoechoic, usually oblong thickening of the intestinal muscle.
The intestinal walls are generally visualized with TV approach up to the proximal sigma/distal descending colon, in conditions of adequate acoustic window. Intestinal nodules should be measured in the three orthogonal diameters, including the depth of infiltration (anteroposterior diameter).
Furthermore, the percentage of circumference involved, the degree of stenosis, the distance of the caudal boundary of the nodule from the margin of the anus can be evaluated [1].

3.2.2 Bladder endometriosis

Ureteral endometriosis may be a consequence of an intrinsic localization of the disease (endometriosis that infiltrates the muscle) or be caused by a peri-ureteral nodule with ureteral involvement. Both the localizations can cause hydroureteronefrosis.
In the evaluation of infiltrating endometriosis of the anterior/lateral/posterior parametrium it is appropriate to verify the relationship of the lesion with the intrapelvic tract of the ipsilateral ureter in order to identify a possible involvement. In case of doubt, pyelectasis should be verified through trans-abdominal route for the identification of patients with functional impairment of the urinary tract.

1) Reid S, Lu C, Casikar I, Reid G, Abbott J, Cario G, Chou D, Kowalski D, Cooper M, Condous G. **Prediction of pouch of Douglas obliteration in women with suspected endometriosis using a new real-time dynamic transvaginal ultrasound technique: the sliding sign**. Ultrasound Obstet Gynecol. 2013;41:685-91.

3.3 Medical terapy

3.3.1 Medical therapy in different location.

In the case of urinary endometriosis and, in particular, in case of symptoms related to bladder endometriosis, there is evidence on the efficacy of progestins (dienogest) [1] or GnRH analogues [2].
A prospective study of 500 women who underwent

surgical treatment for intestinal endometiosis showed a low percentage of recurrence (7.8% in 2-6 years). The percentage of recurrence of disease was lower in women who undergo progestin therapy after surgery (1%) or who had suspended it for a pregnancy (2%). In women who stopped treatment without getting pregnant ,the recurrence rate was 20% [3]. After surgery the goal of hormonal therapy is to prevent the recurrence of the disease and to prevent and treat the painful symptomatology [4].

Although most of the evidence regarding the role of medical therapy in preventing recurrences after surgery focuses on ovarian endometriosis, hormonal treatment should be considered also in case of deep infiltrating endometriosis.

There is no definitive evidence on the superiority of a drug on the prevention of recurrences, but the limitation must be made on the basis of the possibility of long-term adhesion and side effects, taking into account also woman's preferences.

Recommendation	Level of evidence	Strength of recommendation
Long term hormonal treatment is useful in pain control and disease progression	I	A
Progestins are the first line treatment	I	A

1) Angioni S, Nappi L, Pontis A, et al. **Dienogest. A possible conservative approach in bladder endometriosis. Results of a pilot study**. Gynecol Endocrinol 2015;31:406–8.-

2) Fedele L, Bianchi S, Montefusco S, Frontino G, Carmignani L. **A gonadotropin releasing hormone agonist versus a continuous oral contraceptive pill in the treatment of bladder endometriosis**. Fertil Steril 2008;90:183–4.

3) Donnez J, Squifflet J. **Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules**. Hum Reprod 2010;25:1949–58.

4) Somigliana E, Vercellini P, Vigano P, Benaglia L, Busnelli A, Fedele L. **Postoperative medical therapy after surgical treatment of endometriosis: from adjuvant therapy to tertiary prevention**. J Minim Invasive Gynecol. 2014;21:328–334.

3.4 Surgical Therapy

3.4.1 Surgical Therapy in different location

Indications to surgery are:

- failure of and/or controindications to medical therapy
- functional organ damage (Bowel subocclusion/occlusion, urinary tract impairment with renal function compromission)

Surgical techniques for the treatment of Bowel endometriosis include excision of the endometriotic infiltrating lesion by nodulectomy (shaving or discoid resection) or by segmental resection.

There are no guidelines to determine in which cases segmental resection should be performed. Instead of conservative tecnhniques, many operators base their choice on the anatomic localization of the disease and clinical symptoms. Whenever possible, nodulectomy should be the procedures of choice [1,2]. However, there are some cases in which shaving or discoid resection are not feasible and segmental resection should be performed [3,4]: multiple nodules, single nodule with longitudinal diameter greater than 3 cm and/or single nodule with deep infiltration of muscularis layer. In such cases, in fact, nodulectomy techniques could be unsatisfactory in terms of risk of excessive residual disease and an higher rate of complications.

Laparoscopic segmental Bowel resection is a safe and feasible technique with low complication rate when performed by expert operators with proper preoperative indications [4,5]. The risk of peri and postoperative complications is greater in the case of low or ultra-low anastomosis compared to the level of the anal verge and in case of simultaneous opening of the vaginal wall. The use of a transient ileum-or Colostomy protection is discretionary.

Concerning ureteral endometriosis, it is generally accepted that an intrinsic localization of the disease requires ureteral resection with reanastomoses or bladder reimplantation, whereas in the case of extrinsic involvement usually ureterolisis can be feasible [6]. Ureteral endometriosis can be silent but even in asymptomatic cases can lead to the loss of renal function [7], so if diagnosed it requires surgical approach. In case of bladder endometriosis the main indications for surgery are pain and urinary symptoms refractory to medical therapy [8].

The standard surgical treatment for bladder endometriosis is segmentary bladder resection. Laparoscopic shaving procedures are feasible only for superficial peritoneal disease. Cystoscopic treatment must be avoided.

Recommendation	Level of evidence	Strength of recommendation
Absolute indication to surgery are: - failure of and/or controindications to medical treatment in symptomatic patients - Bowel occlusion - Hydroureteronefrosis	V	B
The surgical tecnique should be choosen according to dimension of the lesion and symptoms	V	B
Conservative surgery should be considered in selected cases	IV	C
Continuous hormonal treatment should be considered after surgery	II	A-B

1) Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. **Deep endometriosis: definition, diagnosis, and treatment**. Fertil Steril 2012;98: 564–71.

2) Donnez J, Squifflet J. **Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules**. Hum Reprod 2010;25:1949–58.

3) Abrao MS, Petraglia F, Falcone T, Keckstein J, Osuga Y, Chapron C. **Deep endometriosis infiltrating the recto sigmoid: critical factors to consider before management**. Hum. Reprod. Update 2015 May-Jun.

4) Malzoni M, Di Giovanni A, Exacoustos C, Lannino G, Capece R, Perone C, Rasile M, Iuzzolino D. **Feasibility and safety of laparoscopic assisted Bowel segmental reection for deep infiltrating endometriosis: a retrospective cohort study with description of technique**. J Minim invasive Gynecol. 2016 May-Jun.

5) De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. **Bowel resection for deep endometriosis: a systematic review**. BJOG 2011;118: 285–91.

6) Cavaco-Gomes J, Martinho M, Gilabert-Aguilar J, Gilabert-Estélles J. **Laparoscopic management of ureteral endometriosis: A systematic review**. Eur J Obstet Gynecol Reprod Biol. 2016; 210:94-101.

7) Langebrekke A, Qvigstad E. **Ureteral endometriosis and loss of renal function: mechanisms and interpretations**. Acta Obstet Gynecol Scand 2011; 90(10):1164-6.

8) Schonman R, Dotan Z, Weintraub AY, et al. **Deep endometriosis inflicting the bladder: long-term outcomes of surgical management**. Arch Gynecol Obstet 2013;288:1323–8.

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Psychological impact of gynecological diseases: the importance of a multidisciplinary approach

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ABSTRACT
Gynecological diseases are among the most common disorders diagnosed in the female population and may have a negative impact on quality of life and psychological well-being of the affected women. The aim of this mini review is to investigate the psychological consequences of some of the most common gynecological diseases in order to underline the importance of a psychological approach for gynecological patients and improve therapeutic compliance and quality of life.

Keywords: gynecology, psychology, sexuality, quality of life.

SOMMARIO
Le patologie ginecologiche rientrano tra i disturbi più frequentemente diagnosticati nella popolazione femminile e possono avere un impatto negativo sulla qualità di vita e il benessere psicologico delle donne che ne sono colpite. Lo scopo di questo lavoro è quello di indagare le conseguenze psicologiche di alcune delle più frequenti patologie ginecologiche al fine di sottolineare l'importanza di un approccio mutidisciplinare per le pazienti ginecologiche e migliorare la compliance terapeutica e la qualità di vita.

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Gynecological diseases are among the most common disorders diagnosed in the female population. These conditions are often associated with high stress and have a negative impact on quality of life and psychological well-being of women affected. The psychological impact depends on the level of severity of the disorder and on how much the symptoms interfere with occupational and social activities. In many cases, gynecological disorders can be considered disabling conditions that significantly affect women's everyday life, social relationships, sexuality and mental health. The aim of this brief commentary is to show the psychological repercussions of some of the most common gynecological diseases in order to underline the importance of a psychological approach for gynecological patients to improve therapeutic compliance and quality of life.

Gynecologic cancer is certainly the condition that has the greatest impact on quality of life and psychological well-being of women affected [1–4]. It has been estimated that gynecologic cancer has an incidence of 17% in the world [1]. Endometrial cancer is the most common and has an incidence of 53% [3,5,6]. Ovarian cancer is the second most common gynecologic malignancy and is the leading cause of death among women diagnosed with gynecological cancer in Western countries [7,8]. Multimodal treatments including surgery, chemotherapy and radiotherapy are needed and may be associated with negative consequences in sexual, psychological and social functioning both of women and their partners [1–4,9]. Literature about this topic underlines that diagnosis and treatment of gynecological cancer are often associated with sexual dysfunctions, body image disorders, decreased quality of life, anxiety and depressive symptoms [9–13]. Also partners of women affected can experience sexual and psychological problems because of the distress and the changes within the couple [9,13]. Therefore, a psychological support for women with gynecologic cancer and their partners is fundamental to reduce as much as possible the negative impact of this experience.

Endometriosis is another very common gynecological condition that significantly affects psychological and social functioning of women affected [15,16]. It is a benign and chronic disorder characterized by the by the presence of endometrial glands and stroma outside the uterus [17–20]. The incidence of endometriosis is about 6-10% in women in reproductive age with a peak among women between 25 and 30 years of age [17,19]. Women with endometriosis may suffer from a variety of symptoms including menstrual irregularities, chronic pelvic pain, dysmenorrhea, dyspaurenia, dyschezia and dysuria [18–20]. Several studies about this topic underlined that women with endometriosis show high levels of somatization, depression, sensitivity and anxiety [15,16,21–23]. Moreover, women with endometriosis associated to pelvic pain experience low levels of quality of life and psychological comorbidities may amplify the perception of pain in these patients [19,24,30]. Also in this case, it is evident that a psychological support should be an integral part of the therapeutic process for endometriosis in order to improve the general well-being of women who suffer from this disorder.

Other benign conditions that can compromise quality of life and psychological well-being are uterine fibroids and pelvic prolapse. Uterine fibroids are benign tumors of various sizes that originate from the uterus muscle tissue and have an incidence of 20-50% [24–27]. The most common symptoms of uterine fibroids are bleeding, heavy menstrual periods, anemia, pelvic pain, heaviness and, in some cases, infertility [25]. Literature about this topic investigated the impact of treatments for uterine fibroids on quality of life of the affected women [28,29]. More specifically, hysterectomy has a negative impact on psychological and emotional well-being of the patients, mainly because of the consequent infertility [30,31]. New non-invasive techniques, such as uterine embolization, have recently been developed, improving psycho-physical wellbeing of women who undergo this treatment [31,32]. A psychological counseling is recommended for these patients in order to choose the most suitable treatment and adequately manage its consequences.

Pelvic prolapse is a complex condition defined as the descent of anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina [33]. Cystocele is one of the most common type of pelvic prolapse and is characterized by the pathological herniation of the anterior vaginal wall [33,34]. Prolapse may be associated with a variety of urinary, bowel and sexual symptoms which may significantly compromise the sexuality and quality of life of the patients. In these cases, surgical treatment may significantly reduce the negative impact of the symptoms on quality of life and psychological wellbeing [35–37]. Urinary incontinence is a problem frequently associated with pelvic prolapse and can further reduce the overall well-being of the woman [38–40]. In these cases, it would be appropriate to use validated instruments to assess quality of life of these

patients in order to provide psychological support in high-risk cases.

In conclusion, this brief reflection aimed to demonstrate that women with gynecological problems are often at risk to develop psychological diseases such as anxiety and depression, and to have a poor quality of life. For this reason, psychologists should be involved in a team approach and assist gynaecologists for an adequate management of these diseases.

DECLARATION OF INTEREST

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Nutrition in Pregnancy: three crucial periods for mothers and newborns

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ABSTRACT

It is well recognized that nutritional status during pregnancy is a key factor in modulating the characteristics of the environment within which the foetus originates and develops. Women's nutritional status just before conception and during early pregnancy may influence pregnancy outcomes by affecting critical developmental processes that begin early in pregnancy, as well as the availability of nutrients. Diet has also an important impact on the life of the newborn.

Recent studies showed that the impact of inadequate energy intake and micronutrients intake in pregnancy extends for decades, affecting both mothers and the offspring.

In this paper we review the main evidence on the role of diet in the preconceptional period, in pregnancy and in the post-partum period.

The article focuses on the need for the correct intake of micro nutrients based on the experience of different specialists who follow mothers and their babies (Gynecologist, Obstetrician, Pediatrician and Nutritionist).

Keywords: nutrition in pregnancy, micronutrients, supplementation, breastfeeding.

SOMMARIO

È evidente che lo stato nutrizionale durante la gravidanza sia un fattore chiave nella modulazione delle caratteristiche dell'ambiente in cui il feto origina e si sviluppa.

Lo stato nutrizionale delle donne poco prima del concepimento e durante la gravidanza può influenzare l'esito della stessa condizionando i processi critici di sviluppo che iniziano nelle primissime fasi, così come la disponibilità di nutrienti.

La dieta ha anche un importante impatto sulla vita del neonato.

Studi recenti hanno dimostrato che l'impatto dell'insufficiente assunzione energetica e dell'insufficiente assunzione di micronutrienti in gravidanza si ripercuote per decenni, interessando sia madre che figlio.

In questo articolo vengono esaminate le principali prove sul ruolo della dieta nel periodo preconcezionale, in gravidanza e nel periodo post partum.

L'articolo si concentra sulla necessità della corretta assunzione di micronutrienti in base all'esperienza di diversi specialisti che seguono la madre e il bambino (Ginecologo, Ostetrico, Pediatra e Nutrizionista).

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NUTRITION IN THE PRECONCEPTION PERIOD

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Nutrition in the preconception period is essential in order to improve fertility, promote the mother's ability to meet pregnancy and breastfeeding nutrition requirements. Moreover, nutrition is essential for the healthy development of an embryo, a foetus, an infant, and a child.

The FIGO recommendations, "Think Nutrition first", have recently listed the top six nutrients women need for future motherhood: folic acid, vitamin B12, iron, iodine, calcium and vitamin D. Moreover, the same recommendations emphasize the role of antioxidants in pregnancy outcomes[1].

Folic Acid

Folic acid lowers the risk of birth defects[2]: a recent review by Cochrane[3] confirmed that folic acid supplementation prevents the first and second occurrence of neural tube defects. For women of reproductive age, 400µg/day are recommended as supplements or through fortified foods.

Moreover, there is growing evidence that peripheral levels of folic acid are positively related with the success of assisted reproductive technology (ART) procedures. Two initial studies failed to show an association[4,5], but subsequent large-scale studies showed a significant correlation[6-8].

There is also evidence that the risk of miscarriage is lower in women with higher folic acid levels[9] and that inadequate maternal folate status is associated with low infant birthweight, preterm delivery and fetal growth retardation[10].

Vitamin B 12

Being naturally found in animal products, it is often difficult for vegetarians and vegans to get enough of this nutrient. Higher serum concentrations of folate and vitamin B12 before ART procedures were associated with higher live birth rates among the population exposed to folic acid fortification[7].

Further vitamin B12 level supplementation in the preconception period was associated, with folic acid, with a reduced risk of malformations[11,12].

Iron

Iron is lost with menstruation bleeding and iron requirements are greater in pregnancy. It can be found in meat, liver, nuts, beans, dark leafy greens. Iron deficiency is quite common and is often associated with other nutritional deficiencies; it is the major cause of iron-deficiency anaemia.

A Cochrane review showed that daily oral iron supplementation in pregnant women significantly reduced the risk of low birthweight, and prevented maternal anaemia and iron deficiency in pregnancy[13].

Iodine

Iodine is essential for normal brain development. Moderate and severe foetal iodine deficiency results in substantial to serious developmental delay in children. For example, in a longitudinal study conducted in the UK, 8-year-old children were more likely to be in the lowest quartile of verbal IQ, if their mothers had mild iodine deficiency in early pregnancy, than children of mothers with normal iodine levels[14].

Calcium

Calcium is found in dairy products, canned fish bones, tofu, and beans. Calcium supplementation or foods fortified with calcium before or early in pregnancy and continued at least until mid-pregnancy showed to prevent pre-eclampsia and other hypertensive disorders, maternal morbidity and mortality, as well as to improve foetal and neonatal outcomes[15]. Further calcium supplementation in the second half of pregnancy reduces serious consequences of pre-eclampsia and is recommended by the World Health Organization (WHO) for women with low dietary calcium intake. Most data, however, are based on studies in which calcium supplementation was associated with antioxidants and other supplements.

Vitamin D

Animal studies have shown that mice with 1-hydroxylase deficiency (the enzyme converting 25-hydroxy-vitamin-D [25(OH)D], the vitamin storage form, into the 1,25-di-hydroxy-vitamin-D biologically active form) are infertile and show uterine hypoplasia and the absence of corpus luteum[16]. In humans, it has been shown that the Vitamin D Receptor (VDR) is expressed in the ovary, endometrium and myometrium and that vitamin D deficiency promotes the development of fibroids and endometriosis[17].

Although the role of vitamin D deficiency in human natural fertility has been poorly studied[18-20], several observational data from IVF cycles are available. According to a recent meta-analysis, vitamin D deficiency was associated with decreased chances of a live birth after an IVF/ICSI procedure[21]. Noteworthy, vitamin D deficiency is quite common in the western world. In a study

conducted in Milan, the proportion of women scheduled for IVF with optimal serum levels of vitamin D was below 10% in winter and below 50% in summer[22].

Antioxidants

The levels of vitamins such as vitamin A and vitamin E or Zinc can also affect pregnancy outcomes. The World Health Organization (WHO) recommends vitamin A supplementation during pregnancy in areas where there is endemic vitamin A deficiency, based on the expectation that supplementation can improve maternal and foetal outcomes (including mortality and morbidity) and prevent anaemia, infection and xerophthalmia[23]. The risk of pregnancy complications involving oxidative stress, such as pre-eclampsia, might be potentially reduced by antioxidant supplementation. Furthermore, local development of oxidative stress is believed to have significant adverse effects on the oocyte and the embryo, as well as on implantation (through DNA damage), membrane lipid peroxidation and protein oxidation.

Endometriosis, hydrosalpinx and polycystic ovary syndrome are some conditions that can be potentially caused by oxidative stress in sub-fertile women[24]. Antioxidants are expected to have a protective effect against the detrimental impact of oxygen free radicals. In particular, they can improve epithelial growth in blood vessels and in the endometrium[25]. Recently, antioxidant supplementation showed to improve success rates among women attending clinics for ART[26].

The need for supplementation

It has always been thought that the Italian population is characterized by a high consumption of fruits and vegetables, and, consequently, by an adequate vitamin and other micronutrients intake, but this is not true.

For example, in a cross-sectional study conducted in Milan[27] on women observed in an infertility clinic, only 69% and 44% of women showed adequate levels of homocysteine and vitamin B12, respectively. Serum folate was appropriate in 78% of the study participants, but only a minority (12%) had a concentration of RBC folate considered as optimal for the prevention of fetal neural tube defects. Vitamin B12 levels were also found to be inadequate. Likewise, an analysis by Zappacosta et al.[28] conducted on a group of Italian blood donors found that, among women mainly of childbearing age who did not use folic acid supplements, only 30%, 23%, 25% and 15% had adequate levels of serum folate, RBC folate, homocysteine and vitamin B12, respectively. With regard to the RBC folate threshold considered as optimal prior to conception (400ng/ml), none of the participants had adequate levels. Similar data also emerged in a study conducted on pregnant women[29].

Iodine levels are also inadequate. In a study conducted in the urban area of Cassino in 2016-17, the majority of pregnant women and their foetuses was not protected from the detrimental consequences of iodine deficiency. Therefore, the identification of new strategies to increase the knowledge and awareness of the general population regarding the beneficial effects of iodine supplementation during pregnancy is highly required[30].

All these data underlined the role of supplementation in women who are planning for a pregnancy.

NUTRITION DURING PREGNANCY – THE 1000 DAYS WINDOW

H. Cena

Scientific evidence confirms that the phenomena occurring in the early stages of life play a major role in fostering the development of chronic diseases later on in offspring, underlining the high relevance of "the maternal environment" impact on the life of the future child; therefore, it is universally acknowledged that nutritional status during pregnancy is a key factor in modulating the characteristics of the environment within which the foetus originates and develops. Women's nutritional status just before conception and during early pregnancy may influence pregnancy outcomes by affecting critical developmental processes that begin early in pregnancy, as well as the availability of nutrients[31].

Therefore, awareness of the relationship between nutrition and health in women of childbearing age should be raised, and this life period should become an opportunity for changes towards healthy lifestyles, providing optimum conditions for the present and future health of both the woman and her child. Since nutrition during the critical periods of preconception, conception, implantation, placentation and embryo- or organogenesis may influence pregnancy outcomes by altering both maternal and foetal metabolism, attention should be paid to nutrition also in the preconception period, in order to decrease adverse

pregnancy events such as pre-eclampsia and foetal growth outcomes. Recent studies showed that the impact of inadequate energy intake and micronutrients intake in pregnancy extends for decades, affecting both mothers and the offspring. Both over-nutrition and under-nutrition during pregnancy expose the newborn to the risk of impaired functional capacity in response to extra-uterine metabolic adaptation requests[32].

Underweight women are exposed to greater risk of abortion in the first three months, and in case of malnourishment the foetus can be exposed to adaptive inability. Because malnutrition is a problem affecting not only developing countries but also developed countries, particular attention should be paid to women with a history of Eating Disorders, to adolescents, to those with a low SES (Socio Economic Status) and to those who had undergone a bariatric surgery procedure for morbid obesity[33].

On the other hand, maternal obesity with high pre-pregnancy BMI or excessive weight increase during pregnancy, impacts pregnancy outcomes leading to the development of gestational hypertension, preeclampsia and gestational diabetes and induces both short-term effects on the foetus and the newborn, such as a twofold increased risk of delivering an infant with neural tube defects (NTDs)[34], and long term ones affecting health during childhood, independently of other maternal comorbidities[35].

Several studies described a positive association between elevated BMI and the risk of birth defects. Data on plasma concentration of folate in pregnant women with obesity showed values far below those recommended, regardless of the diet, while folate levels should increase before pregnancy to reduce neural tube defects, therefore folate status in women of childbearing age with obesity should be assessed to start personalised and more adequate supplementation before conception[36] and during pregnancy.

Moreover, recent studies demonstrated that maternal obesity during pregnancy is associated with alterations in the composition and diversity of the intestine microbial community[37], influencing the microbial colonization and increasing the risk of metabolic diseases in the offspring[38]. This scenario may be particularly serious for obese women of childbearing age who may be subject to an increased risk of key nutrient deficiencies and inadequacies related to negative pregnancy outcomes[39]. Therefore, it is important to advise pregnant women to monitor their weight gain in pregnancy[40]. During pregnancy, there is a higher daily energy demand due to increased expenditure and basal metabolic rate, caused by the placenta development, foetus growth, increased size of maternal organs, increased respiratory and cardiovascular work; so, the energy intake will need to be valued for each specific case on the basis of the actual daily energy expenditure, depending also on physical activities. Energy requirements should be met taking into account pre pregnancy BMI and the desirable weight gain according to the national reference values[41]. 2014 reference intake levels for energy intake for the Italian population (LARN) 2014 suggest additional requirements of 69 kcal/day for the first quarter, 266 kcal/day for the second and third 496 kcal/day trimester of pregnancy (for an overall total of 76,530 kcal). Values very similar to those established by EFSA (European Food Safety Authority): 70 kcal/day in the first trimester, 260 and 500 kcal/day in the second and third trimester, respectively[42].

Food choices should be based on protein intake, dietary fats, vitamins and minerals. It is recommended to maintain an adequate intake of protein, whose requirements increase significantly from the second trimester, by eating fish, lean meats, eggs, dairy and legumes. An increased intake of proteins is required especially during the second and third trimester, and 21 grams per day are required for maternal tissues, placenta and foetal growth[41].

During pregnancy, attention should also be paid to macronutrients, such as long chain n-3 polyunsaturated fatty acids (LC-PUFA), which play a critical role in foetal and infant growth and development. Maternal n-3 LC-PUFA supplementation may reduce the risk of early preterm birth (>34 weeks) and seems to be very promising for primary allergy prevention during childhood[43]. Since the LC-PUFA required by the foetus is supplied by preferential placental transfer of preformed LC-PUFA, rather than their precursor, it was hypothesized that additional maternal supply of LC-PUFA, especially DHA, during pregnancy may improve maternal and infant outcomes[43]. An association among n-3 fatty acids, serotonin transporter genotype, and postpartum depression was identified[44], so diet quality, dietary intake of n-3 fatty acids, and overall nutritional status can impact the risk of postpartum depression[45].

Although consumed in small quantities, vitamins and minerals play a key role, for human health; this role is even more important during pregnancy and breastfeeding, to the extent that

micronutrients requirement increases more than those of macronutrients. An inadequate intake of micronutrients, as well as poor nutritional diet variety, can have serious consequences for both the mother and the developing foetus.

Micronutrients such as iron, zinc, iodine and, as B-vitamins, vitamin A, folic acid and zinc influence oxidative pathways and methylation, and also affect embryogenesis, which occurs early in pregnancy and may be related to miscarriage and foetal malformations.

It is recommended to vary often the choices of fresh fruits and non-starchy vegetables (both yellow-orange and dark green leafy products), consume cereals (pasta, rice, barley, bread, etc.) on a daily basis, olive oil as a dressing and reduce consumption of salt preferring iodized one.

Furthermore, folic acid–containing supplements proved to reduce the incidence of first occurrence of NTDs, and are recommended globally before and in early pregnancy, while vitamin D supplementation during pregnancy reduces the frequency of baby low-birth-weight[39]. A meta-analysis of 31 observational studies and 4 RCTs conducted by Wolf et al.[46] evaluated the effect of multivitamin and mineral supplementation on pregnancy outcomes in developed countries, reporting a significant decreased risk of NTD recurrence, lower for gestational age infants, cardiovascular defects, urinary tract defects, and limb deficiencies.

Pregnant women also need to maintain an adequate level of hydration and avoid consumption of alcohol[47]. Alcohol consumption in pregnancy may increase the risk of miscarriage, intrauterine growth retardation, prematurity, low birth weight, and lead to neurodevelopment impairment later in life[45]. Beverages containing substances such as caffeine are to be consumed with caution too; moreover, both artificially sweetened and sugar-sweetened beverage have been recently reported to be associated with infant BMI[48]. Given the current epidemic of childhood obesity and widespread use of artificial sweeteners, dietary recommendations for pregnant women should also suggest what kind of beverages are to be limited or excluded during pregnancy. Pregnancy has been regarded as a maternal phase with requisite additional nutritional requirements and can prevent short and long term adverse events.

One of the most discussed issued is diet during pregnancy for food allergies prevention. Scientific evidence showed that there were no benefits from the restriction of food allergens in the diet of pregnant (and breastfeeding) women from 'high risk' families with a family history of allergic diseases; in unselected samples ("normal risk families") the level of evidence is such that specific dietary restrictions for women during pregnancy cannot be recommended as a preventive strategy[49]. Since there is no consensus on the most effective strategy for the prevention of food allergies in newborns, we should consider the national guidelines[50] on this topic, which advocate moderate consumption of foods rich in pharmacologically vasoactive molecules or capable of releasing them, including fermented cheeses, shellfish, clams, cocoa/chocolate, that can trigger adverse reactions.

The composition and the diversity of the intestinal microbiota heritage are defendants in the multifactorial aetiology of allergic pandemic expansion, and the delivery method and the type of feeding are decisive for the postnatal bacterial colonization and the future composition of the gut microbiota. Nutrition during pregnancy plays a key role in the development, maintenance, and optimal functioning of immune cells and microbiota diversity. Nutrients, such as zinc and vitamin D and nutritional factors, such as pre- and probiotics, can influence the nature of an immune response and are important in ensuring appropriate functioning of the immune system[51]. Moreover, evidence is emerging regarding the role of fats and maternal n-3 LC-PUFA supplementation, which showed to reduce the risk of primary allergy during childhood[43].

The aim of prenatal nutrition is to support a healthy uterine environment for optimal foetal development while supporting maternal health. The ideal prenatal diet should limit overconsumption for the mother and prevent under-nutrition for the foetus[52].

With respect to the Italian population, the available data show that intakes of selected nutrients are often insufficient for both target population groups and pregnant and breastfeeding women[53]. This applies, in particular, to micronutrients like iron, iodine, calcium, folic acid, vitamin D as well as fats like DHA.

Therefore, besides a healthy lifestyle during pregnancy, which includes a balanced nutrition-focused diet, regular physical activity, food safety and hygiene practices and avoidance of harmful habits like smoking, alcohol or caffeine and/or sugar rich drinks consumption, supplementing vitamins, minerals and DHA are recommended, plus any additional vitamins or minerals if any deficiencies are detected. Supplements do not

replace a healthy diet, but ensure that a woman is receiving enough daily nutrients[54] and should always be considered, in particular, for women on exclusion diets, smokers, adolescents, for those with weight problems, multiple or close pregnancies, and previous unfavourable pregnancy outcomes, due to the increased risk of inadequate supply of nutrients to support maternal and infant health[36,43,53,54].

POSTPARTUM NUTRITION

D. Corvino

Often, the well-being of pregnant women, including nutritional aspects, is neglected immediately after childbirth when biological, hormonal and lifestyle changes require adequate support. In particular, meeting the increased energy and nutrient requirements, protecting the mother's health and promoting a regular growth of the newborn are objectives to be pursued in line with a healthy lifestyle.

Stress and physical and mental fatigue, associated with feelings of inadequacy and a lack of time for personal care and the preparation of proper meals often induce new mothers to neglect their own diet, which translates into frugal meals, long hours of fasting, unhealthy food choices, consumption of ready meals or junk-food, poor nutritional quality foods, high fat and high sugar meals with no adequate amounts of micronutrients recommended for the well-being of every woman and her baby after delivery. Often new mothers, in an attempt to return to their pre-pregnancy fitness, follow miraculous restrictive, unbalanced diets poor in vitamins and minerals that do nothing but increase the level of stress.

As it happens with pregnancy, in fact, the nutritional needs for new mothers change not only in terms of energy and macronutrients, but also and above all in terms of micronutrients. For some of them – such as calcium, phosphorus, magnesium - the requirement remains as high as in pregnancy[47] given the important function for the growth and formation of bones, which consist mainly of these components, their involvement in energy and metabolic processes, as well as in neuro-muscular transmission. Vitamins are also essential micronutrients; in particular, among fat-soluble vitamins, vitamin D, which is essential for calcium absorption, and among water-soluble vitamins, vitamin B12, which is essential for preventing and/or correcting anaemia, often associated with the postpartum period and for its "neurotrophic" action that mitigates susceptibility to psycho-physical stress. Being contained exclusively in foods of animal origin, vitamin B12 must necessarily be integrated into vegetarian and vegan women, often not well informed of the real risks induced by prolonged vitamin B12 deficiency, not only for them but also for children. With regard to anaemia prevention, for new mothers, vitamin C requirements also increase, since it favours the absorption of iron and of vitamin B6, whose role in the degradation of homocysteine makes it an essential vitamin for the prevention of cardiovascular diseases (venous thrombosis) and of depression symptoms often characterising the postpartum period[55].

Due to its important antioxidant and photo-protective function, as well as its role in the prevention of retinopathies in premature infants, lutein is also extremely important[56].

Contained in green leafy vegetables, lutein bioavailability is also high in broccoli, potatoes, asparagus, and breast milk is also characterized by high concentrations of lutein. So, during breastfeeding, taking this beta carotenoid is as important as taking calcium (by intake of water with a high content), iodine (using little and iodized salt), zinc, copper, selenium, vitamin A, B vitamins, vitamin C and an adequate quantity of proteins[47]. During this period, it is recommended to reduce the consumption of foods, such as onion, garlic, asparagus, spices, and so on, that can alter the taste of milk and affect breastfeeding. Maintaining an adequate level of hydration during pregnancy, and even more during breastfeeding with water, tea, or rather caffeine free tea, herbal teas or other unsweetened drinks, is crucial, not only when feeling thirsty[41]. In fact, milk production is metabolically expensive in terms of water consumption, because the latter is the major component of breast milk in which all other nutrients are dissolved. The LARN, the Reference Levels of Nutrient and Energy Intake for the Italian Population, recommend a surplus of about 700ml of water compared to consumption during pregnancy (2000ml/day). Its function on fluid homeostasis, transport of useful substances and the elimination of catabolites, as well as on maintenance of body temperature, just when the hormonal structure changes significantly, make it an essential component even in the postpartum period. Alcohol consumption, on the other hand, should always be avoided in the postpartum period, as well as during pregnancy: 15 minutes after taking alcohol, the alcohol level in the

foetus is similar to that of the mother. During breastfeeding, alcohol is quickly and easily distributed from the blood to milk and then to the baby. Alcohol can also reduce the production of breast milk[47,57,58].

A proper nutrition, the right information and an integration of the micronutrients required for healthy and balanced maternal nutrition, allow to meet the nutrition requirements for new mothers in a delicate and demanding period, that is after childbirth, whether the baby is breastfed or not, because the assumption that a mother who eats well is a healthy mother and will have a baby who will eat well in the future is still valid.

NUTRITIONAL NEEDS DURING BREASTFEEDING

A. Lops

There is new important knowledge about nutritional needs during the breastfeeding period. 2014 LARN (Reference Levels of Nutrient and Energy Intake for the Italian Population)[41] provide new reference values for energy and nutrients, also considering some "delicate" periods in life, such as breastfeeding.

During breastfeeding, as well as during pregnancy, an increase in maternal energy needs must be expected, necessary for the production of milk, whose caloric density is determined primarily by the fat content.

The additional energy requirement for breastfeeding women is related to the quantity of milk produced. 2 to 3 weeks after childbirth, a nursing mother generally provides the infant with 500 to 600ml of milk every day, which can then increase up to 850ml. Although very variable from woman to woman, the synthesis of milk can is approximately 810ml per day, on average, an amount that decreases progressively during weaning. To ensure adequate milk production, nursing mothers need to increase their daily intake of calories by 500 kcal/day. An insufficient energy intake during breastfeeding mainly leads to a reduction in the volume of the milk produced, which changes only minimally in terms of composition.

Although found in diets in reduced amounts, micronutrients (vitamins and minerals) play a basic role for body functions, becoming even more important during pregnancy and breastfeeding. Micronutrient requirements, indeed, increase more than those of macronutrients[53].

Iron

As postpartum bleeding increases the probability of maternal anemia, even in industrialized countries almost 50% of women need iron supplementation at this stage.

The secretion of iron in milk is rather limited, therefore WHO (World Health Organization) and FAO (Food and Agriculture Organization of the United Nations) support a decrease in iron intake during breastfeeding, compared to other fertile stages, to compensate for amenorrhea.

In the absence of menstruation, women should take 11mg/day to be increased to 18mg/day in case of return of menstruation.

Iodine

During breastfeeding, iodine requirements increase as a result of changes in maternal metabolism, also to promote milk secretion.

The intake recommended during breastfeeding is 200µg/day, so as to guarantee a iodine content in the milk of about 100 to 150µg/100mL.

Calcium

Calcium maternal requirements are met with a daily intake of about 1000mg. The amount of calcium secreted on a daily basis in breast milk is quite variable (150 to 300mg/day) and depends mainly on the mobilization of calcium from bone deposits. Despite the concurrent reduction of urinary calcium secretion, this results in a temporary loss of bone density during breastfeeding[59].

Some studies showed that calcium secretion in milk is substantially independent of its dietary intake and of supplementation. Therefore, the recommended intake during breastfeeding is not different from that of the healthy adult female population (1.0g/day). However, women with dietary calcium intakes lower than 300mg/day and adolescents, with high basal requirements (1.2g/day according to the RDA) are at risk of deficiency also during breastfeeding.

Vitamin D

Even during breastfeeding, the risk of vitamin D deficiency is mainly for ethnic groups with hyper-pigmented skin or with low exposure to sunlight, given the influence of sunlight exposure on vitamin D metabolism. Vitamin D food intake is usually sufficient, but may be inadequate, particularly in situations of greater needs and in countries where food sources are reduced. An intake of 15µg/day (600IU/day) is necessary to meet the requirements of this vitamin during

breastfeeding. These levels can be increased up to 1000-2000IU/day in case of vitamin deficiency risk factors for the duration of breastfeeding.

However, breast milk amounts of vitamin D (<80 IU/l) are not enough to prevent vitamin D deficiency in the first year of life[60]. Maternal supplementation is not considered sufficient for the needs of the newborn, who must therefore be directly supplemented.

Folate

Folate concentrations in breast milk progressively increase from colostrum to mature milk, to much higher levels than plasma. The absence of a correlation between maternal and milk status suggests an active role of the mammary gland in the transport and regulation of folate secretion, only marginally influenced by dietary intake[61].

During breastfeeding, folate intake should be increased by 25%, up to 500µg/day[62].

The concentration in breast milk of many other vitamins (thiamin, riboflavin, vitamin B6, vitamin B12, vitamin A) depends on maternal vitamin levels: a maternal vitamin deficiency usually corresponds to human milk deficiency.

DHA

Although it is not a micronutrient, special attention should also be paid to DHA.

DHA is the major polyunsaturated fatty acid contained in the human brain and retinal rods, it plays major roles in the psychomotor neurodevelopment in the first months of life, when it is supplied at high amounts by breastmilk.

The benefits of DHA for the foetus and for the infant are supported by an extensive literature, which confirms the importance of appropriate omega-3 intake for maternal health, for the composition of breastmilk, and for overall infant health[63]. According to EFSA and the Italian RDA, DHA requirements increase to 100 to 200mg per day during pregnancy and breastfeeding.

There is some evidence that approximately 80% of the population (also in Italy) does not ingest the daily amount of EPA and DHA recommended by international guidelines (250 to 500mg daily).

The consumption of two servings of fish per week allows to get the adequate DHA content in breastmilk. The EFSA report concludes that consumption of more than 3 to 4 servings of fish/week does not provide any additional benefit. In order to balance adequate amounts of EPA and DHA and lower the risk of environmental contaminants, smallest fish such as sardines, anchovies and mackerel should be preferred[64].

CONCLUSION

Maternal good nutrition during the preconceptional period and pregnancy and good nutrition of children in the earliest years it are essential for lifelong health. They provide the building blocks for brain and immune system development and healthy growth[59].

From the review it is clear that the supplementation of micronutrients is necessary in all three stages of pregnancy. Supplementation is not intended as a substitute for proper nutrition but as an aid to maintain adequate nutritional intake. Women and parents need and deserve practical and trustworthy information on nutrition. Gynecologists, Obstetricians, Pediatricians and Nutritionists play an important role in providing this information.

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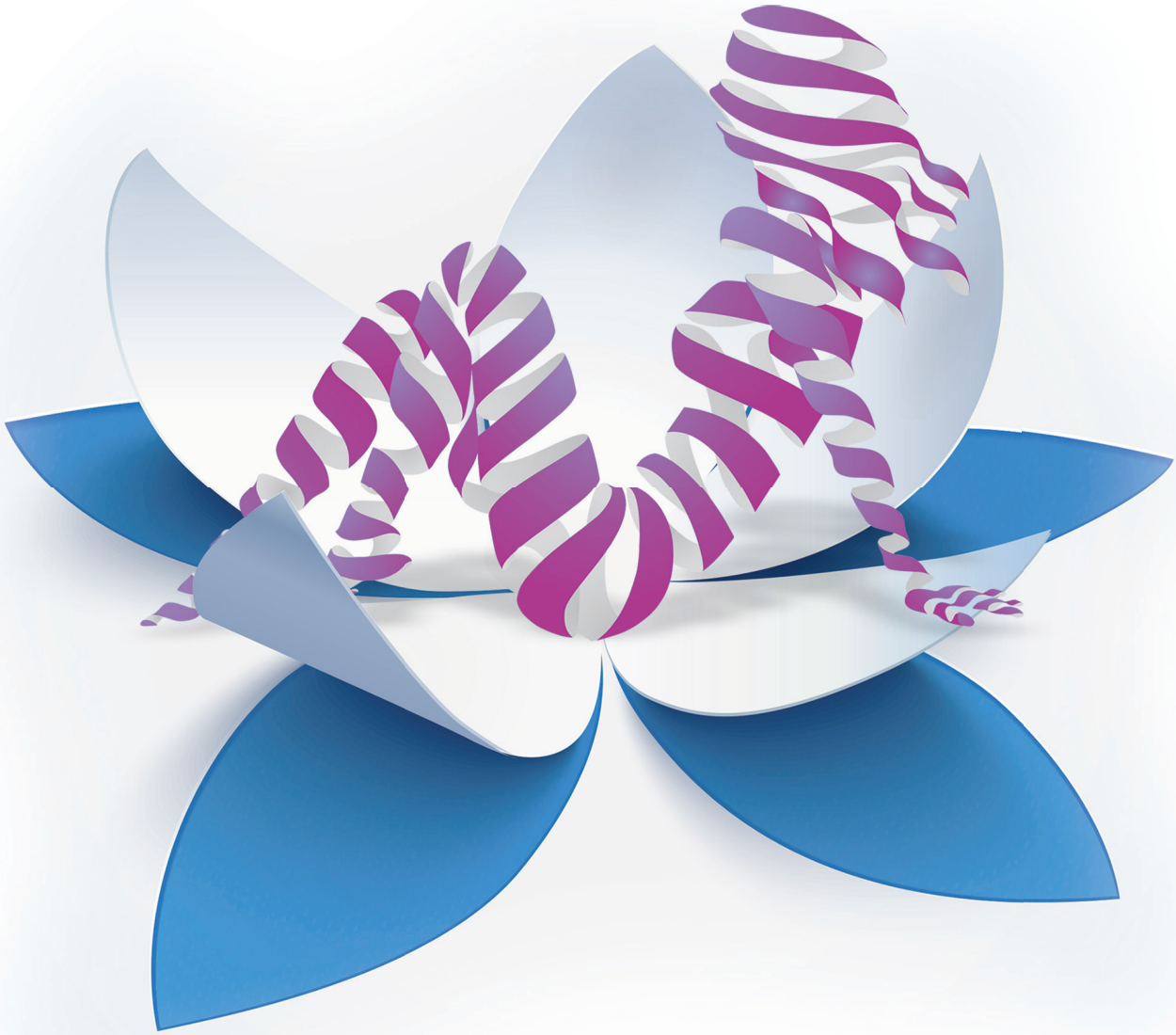

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Evaluation of implantation and clinical pregnancy rates after endometrial scratching in women with recurrent implantation failure

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ABSTRACT

Objective: to investigate the role of endometrial scratching to improve clinical pregnancy and implantation rates in women with repeated implantation failure.

Methods: 80 patients with at least two previous failed ICSI or FIVET (failed implantation) were randomly assigned to group 1 (scratching) or group 2 (control). Endometrial scratching was performed by pipelle de Cornier® while the control group was submitted to a sham procedure using an embryo-transfer catheter. All of patients underwent to estroprogestin pill (ethinylestradiol 30 µg + levonorgestrel 150 µg) during the month before ovulation hormonal induction and IVF. Implantation and clinical pregnancy rates were compared for Mantel-Haenszel Risk Ratio test ($p < 0.05$).

Results: endometrial scratching was associated with higher clinical pregnancy (25% vs. 10%, p=0.08) and implantation (40% vs. 33%, p=0.67) rates but the comparison between the two groups was not significant.

Conclusion: endometrial scratching in the patients with repeated implantation failure during the cycle before ovarian stimulation doesn't significantly improve implantation and clinical pregnancy rates.

Keywords: scratching, in vitro fertilization, implantation, pregnancy, failure.

SOMMARIO

Obiettivo: indagare il ruolo dello scratching endometriale nell'aumentare i tassi di gravidanza clinica e di impianto nelle pazienti con multipli fallimenti dell'impianto dopo fecondazione assistita.

Materiali e metodi: 80 pazienti con almeno due precedenti ICSI o FIVET fallite (fallimento dell'impianto) sono state randomizzate e assegnate al gruppo 1 (scratching) o al gruppo 2 (controllo). Lo scratching endometriale è stato eseguito con pipelle de Cornier® mentre nel gruppo di controllo la procedura è stata simulata con un catetere da embryo-transfer. Tutte le pazienti sono state sottoposte a trattamento estroprogestinico (etinilestradiolo 30 µg + levonorgestrel 150 µg) il mese precedente alla stimolazione ovarica e alla IVF. I tassi di impianto e di gravidanza clinica sono stati confrontati con il test Mantel-Haenszel Risk Ratio ($p<0.05$).

Risultati: lo scratching endometriale è associato a tassi migliori di gravidanza clinica (25% vs. 10%, p=0.08) e di impianto (40% vs. 33%, p=0.67) ma il confronto tra i due gruppi è risultato non statisticamente significativo.

Conclusioni: lo scratching endometriale eseguito nelle pazienti con ripetuti fallimenti dell'impianto durante il mese precedente alla stimolazione ovarica non aumenta significativamente i tassi di impianto e di gravidanza clinica.

Parole chiave: scratching, fecondazione in vitro, impianto, gravidanza, fallimento.

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INTRODUCTION

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are the most frequent methods used for treating infertile couples; these techniques can be performed using fresh or frozen embryos, in which it is necessary a thawing process prior to transfer[1].

A cycle is defined as canceled when after ovarian stimulation there is not in utero transfer. A cycle can be canceled before withdrawal of oocytes (suspended cycle) or before embryo transfer (interrupted cycle). 17.354 canceled cycles were reported in Italy in 2015, representing 31,4% of all cycles with a 2,8% increase compared to 2014. 9,2% (+0,4 %) were suspended before pick-up and 22,1% (+2,3%) were interrupted before embryo transfer. From 2005 a 20% decrease of suspended cycles and a 86% increase of interrupted cycles have been registered[2].

The main reason of suspension is the absence of response to ovarian stimulation, occurring in 2/3 of canceled cycle, while 11,8% of suspensions are caused by abnormal response to ovarian stimulation. This suspension can be determined by many factors and it is directly proportional to age of patients. In fact, up to 39 years the possibility of suspension after pick-up is less than 10%, in the patients aged between 40 and 42 years the risk of suspension is 10,1% and in the patients aged more than 43 years the risk is 2,5 higher than younger patients[3].

The mean reasons of interruption are missed fertilization (22,4%) and miss oocytes' withdrawal (17,1%): both determines about 40% of interruptions. About 40000 embryo-transfer were reported in Italy in 2015 and pregnancy was obtained in 27% of cycles. The probability to get pregnant depends on multiple factors that can be summarized in two elements[4]:

- Embryonal factor: quality and quantity of transferred embryos;
- Uterine cavity: endometrial receptivity, uterine malformations and uterine disease as fibroids and polyps.

Histological and pathological changes induced by ovarian hormones during luteal phase are biomarkers of endometrial receptivity. Their expression, evaluated with endometrial biopsies, could be very useful for the study of endometrial receptivity[5].

It's been proposed to perform mechanical lesions of endometrial mucosa (biopsy/scratching or hysteroscopy) in the previous cycle or during ovarian stimulation for IVF in order to increase implantation rate in women with RIF (Repeated Implantation Failure)[6-9]. The results of systematic revision highlighted a positive effect of local lesions on endometrial mucosa in the cycle before ovarian stimulation for IVF[10]. It's been theorized that mechanical injury activates immunologic and genetic changes on endometrial mucosa with better endometrial receptivity for implantation[11,12].

The aim of this study is to evaluate the role of endometrial scratching in the patients with RIF in order to increase implantation and clinical pregnancy rates.

MATERIALS AND METHODS

It's been performed a randomized unblinded controlled trial (RCT) in a ratio of 1:1. We evaluated infertile couples to undergo in vitro fecundation at the Medically Assisted Procreation Centre of Obstetrics and Gynecologic Operative Unit, Cannizzaro Hospital (Catania, Italy). 80 patients were recruited according to following inclusion criteria:

- Age between 25 and 37 years:
- Primitive or secondary infertility;
- At least two previous failed ICSI or FIVET (failed implantation) despite easy transfer and good quality of embryos;
- Normal thickness and endometrial ultrasound pattern, defined as absence of intracavitary disease (fibroids, polyps, etc.), with no anamnestic severe deep endometriosis;
- Good quality of seminal fluid of partner and negative anamnesis for relevant diseases;
- Negative genetic, metabolic and infective evaluation.

The procedure and the objective of scratching were explained to all of patients and an informed consent was administered after institutional review board approval.

80 patients were randomly recruited according to inclusion criteria. Descriptive statistics of sample is summarized in **table 1**. All of patients underwent to estroprogestin pill (ethinylestradiol 30 μg + levonorgestrel 150 μg) during the month before ovulation hormonal induction and IVF.

Gynecological examination and transvaginal ultrasound were performed between the 14th and 16th day of pill in order to evaluate size and morphology of uterus, ovaries and to start consequently administration of GnRH agonist (buserelin).

Table 1.
*Descriptive statistics of women undergoing assisted reproduction allocated to endometrial scratching (n=40) or sham procedure (n=40). *Chi-square test. ** Kruskal-Wallis test. CC, clomiphene citrate; FSHr, recombinant follicle stimulating hormone; hMG, human menopausal gonadotropin*

PARAMETERS	ENDOMETRIAL SCRATCHING	SHAM PROCEDURE	P
AGE (MEDIAN)	32	31	** 0.33
PREVIOUS FAILED ICSI OR FIVET	30/40 (75%)	31/40 (77,5%)	* 0.79
2			
3	10/40 (25%)	9/40 (22,5%)	
OVARIAN STIMULATION PROTOCOL	11/40 (27,5)	10/40 (25%)	* 0.95
• CC+hMG + Antagonist			
• FSHr + Agonist	14/40 (35%)	15/40 (37,5%)	
• FSHr + Antagonist	15/40 (37,5%)	15/40 (37,5%)	
N. TRASFERRED EMBRYOS	9/40 (22,5%)	3/40 (7,5%)	* 0.68
1			
2	16/40 (40%)	8/40 (20%)	
≥3	5/40 (12,5%)	1/40 (2,5%)	

Patients were randomly assigned to group 1 (scratching) or group 2 (control). Endometrial biopsy by pipelle de Cornier® (Laboratoires PRODIMED, Neully-EnThelle, France) were performed in the patients of group 1. After disinfection of vagina and portio with iodate solution, the pipelle was introduced gently through the cervix up to the uterine fundus. The piston was then drawn back to the end of the biopsy cannula until it self-locked, creating a negative pressure. Aiming to cover the entire endometrium, the examiner applied regular first back-and-forth movements (3–4 cm) and then rotating the sampler, over the whole uterine cavity, during a period of 30 s. The entire procedure duration was up to 5 minutes. Endometrial scratching was performed by a dedicated team (2 operators only) during luteal period, between 5 and 10 days before menstruation.

The control group was submitted to a sham procedure using an embryo-transfer catheter introduced along the cervix inside the uterine cavity. A visual analog scale consisted of an horizontal line between 0 (no pain) and 10 cm (worst pain) was administered to all of patients. Each patient marked a point on this scale representing the pain related to procedure.

A GnRH analogue was administered together with estroprogestin pill until to HCG intake. Hormonal and sonographic evaluation was performed after 15 days from starting administration of gonadotropins (rFSH and/or HMG) with tailored dose for each patient.

The monitoring consisted of sonographic and hormonal (17- β estradiol, prolactin and LH) control at day 5 after gonadotropins intake and then every other day. The entire gonadotropin therapy duration was between 11 and 12 days. Human Chorionic Gonadotropin (HCG) was used in order to stimulate oocyte's growth with a dose of 5.000-10.000 UI after sonographic evaluation of endometrial thickness (range 8-12,5 mm); oocyte's pick-up was performed after 34-36 hours.

Adequate number of oocytes was obtained from pick-up procedures, without complication. 2 or 3 embryos were transferred in utero 48-72 hours after oocyte withdrawal. Only one case of uterine mucocele 2 day after pick-up was registered, so the embryo-transfer was delayed to the next day, after aspiration of mucocele and evidence of regular sonographic endometrial pattern.

Luteal period support therapy was performed by administration of intramuscular progesterone 50-100 mg/die and vaginal estradiol valerate 2-6 mg/die, up to negative pregnancy test or 12 weeks of gestation. Serum β-hCG was measured out 14 days after embryo-transfer.

Clinical pregnancy is defined as ultrasound evidence of gestational sac with beating heart embryo[13].

We calculated implantation and clinical pregnancy rates and then statistical analysis by SPSS and Excel software for Mantel-Haenszel Risk Ratio test. 0.05 was used as the cutoff value for probability significance ($p < 0.05$).

RESULTS

All of recruited patients completed reproductive procedures including embryo-transfer. 12 of 40 patients of group 1 (endometrial scratching) were positive to β HCG dosage performed 14 days after embryo-transfer; serum β HCG was measured weekly until to 4-5 weeks after embryo-transfer. Then transvaginal sonography was performed. 10 of 12 patients were pregnant: intrauterine gestational sac, yolk sac, vital embryo with regular crown-rump length were detected. Clinical pregnancy rate was 25% (10 pregnancies of 40 patients). 8 pregnancies were singleton and 2 twin gestations. Overall 30 embryos were transferred resulting in 40% implantation rate (12/30) while cumulative implantation rate was 11% (12/108).

In the group 2 (control) 6 of 40 patients were β HCG positive while only 4 of them

had sonographic evidence of pregnancy (vital embryo), so the clinical pregnancy rate was 10% (4 pregnancies/40 patients). Overall 12 embryos were transferred resulting in 33% (4/12) implantation rate while cumulative implantation was 3,5% (4/112).

The comparison of clinical pregnancy and implantation rate between group 1 and 2 was not significant (**table 2**).

Table 2.
Mantel-Haenszel Risk ratio

	Group 1 (scratching)	Group 2 (control)	RR (CI 95%)	P
Clinical pregnancy rate	10/40 (25%)	4/40 (10%)	**0.83 (0.67-1.02)**	0.08
Implantation rate	12/30 (40%)	4/12 (33%)	**0.90 (0.54-1.4)**	0.67

30 of 40 patients declared a pain from 5 to 7, 6 patients a value of 2 and 4 patients a value of 8, so the scratching should be a procedure whit moderate pain. In the control group the median pain was inferior to 5.

Very low bleeding (<50 ml) was registered only during the scratching in the major part of group 1 patients (31/40, 77%).

DISCUSSION

Correlation between endometrial quality in proliferative phase (mostly before the transfer) and probability to get pregnancy was evaluated in the past years since the 90s and sonographic study of endometrium was introduced as uterine receptivity marker[14,15]. Particularly thickness and pattern are the parameters which have to be studied in order to obtain required information[16]. Many publications support at least 7 mm thickness to have good probability of implantation and 2,5 ml is the cutoff volume to get pregnancy established from researches using tridimensional ultrasound[17]. Endometrial pattern evaluation is based on endometrial and myometrial echogenicity in longitudinal section. A "low grade" pattern is correlated with low success rate; it is displayed as homogeneously hyperechogenic without echogenic middle line. Conversely trilaminar pattern is associated with good endometrial receptivity and better conception rates[18].

The Doppler study of uterus vascularization in unfertile women revealed that lower perfusion of uterine and spiral arteries with absent endometrial and sub-endometrial flow causes low probability of implantation[19].

However, many studies investigated other markers of endometrial receptivity as cytokines, interleukins and hormones. High progesterone level before oocyte withdrawal change genetic profile of endometrium during implantation time and molecular way majorly influenced is the cytotoxic way by Natural Killer cells, in which about 16 genes are altered. Particularly 5 of these encode for receptors that are overexpressed on trophoblastic fetal cells when progesterone level is higher, resulting in failing implantation.

It has been demonstrated also that Natural Killer cells levels are positively correlated with some angiogenic steps; overexpression determines oxidative stress and altered placental circulation. Other proteins like cytokines, growth factors, integrins, glycodelin and LIF (Leukemia Inhibitory Factor) have been recognized as predictive of endometrial receptivity, but they are not useful for current clinical activity[20].

Furthermore it's known a positive correlation between pinopodes expression and pregnancy rates in the patients undergone to hormone replacement therapy and egg donation, and also a correlation between lower expression of pinopodes and repeated implantation failures. Studies on endometrial biopsies highlighted higher concentration of pinopodes at 2 cm from uterine fundus, identifying it as preferential situs of implantation[21]. For the major part of infertile couples limiting factor is the implantation, by also little known causes. The term RIF, Recurrent Implantation Failure, used from 1983, represent the absence of implantation or clinical pregnancy after repeated embryo-transfer.

Endometrial receptivity is one of key factors regulating blastocyst implantation and it has been demonstrated that mechanical trauma on endometrial mucosa determines inflammatory response with release of cytokines and growth factors like IL-6 and TNF-α, making endometrium more prepared for implantation[22]. Furthermore it determines genic expression modulation with higher expression of favorable protein for implantation, like MUC1 (mucin 1 transmembrane), crystalline alpha B, APOD (apolipoprotein D), PLA2 (phospholipase A2) and UPIb (uroplakin Ib), glycodelin A, laminin alfa 4, integrin alfa 6 and MMP-1 (metalloproteinases 1), and recruitment of macrophages and dendritic cells playing an important role on decidualization and implantation[23].

This effect is maintained also in the next cycle,

probably because recruited monocytes live and stay longer in the site of interest. In order to improve results in women with RIF, many study have been take in consideration pregnancy rates after local trauma on endometrium in the cycle before ovarian stimulation, including only patients with regular uterine cavity at hysterosalpingography or hysteroscopy. All of these studies showed high clinical pregnancy rates in the patients undergone to hysteroscopy[24-26]. Number of sampling among these studies is different: one time[27], one sampling between 7 and 10 days and then another one 24-25 days after previous cycle[28], 4 times (days 8, 12, 21, 26) in the cycle before ovarian stimulation[29].

Successful of implantation is a complex process that needs a receptive endometrium, good embryos at blastocyst state and synchronization between maternal and embryonal tissues. In order to improve implantation rate, current evidence is that patients should have ready frozen embryos to be successively transferred during a natural cycle. Alternatively endometrial scratching could be performed in the cycle before ovarian stimulation. Number, time and modality of scratching have to be still defined.

In our study clinical pregnancy and implantation rates did not differ significantly between the examined groups. In the literature concerning the role of endometrial scratching to improve clinical pregnancy and implantation rates, there are three not-randomized[26,29,30], and five randomized studies[8,9,28,31,32], demonstrating benefit of this technique.

Our research differs from the other studies for the inclusion criteria, taking into consideration only patients with two or more previous failure. Our results can be compared only with Nastri study of 2013[7], which examined 158 women underwent to estro-progestin treatment and successive endometrial scratching, demonstrating significant improve of clinical pregnancy and birth rates but worse pain score. Despite the limits of our study including poor number of patients and absence of sonographic parameters (endometrial thickness, endometrial volume, uterine Doppler velocimetry), our preliminary data should demonstrate that endometrial scratching in the patients with RIF during the cycle before ovarian stimulation doesn't significantly improve implantation and clinical pregnancy rates.

Currently many questions are still open on endometrial scratching. The precise subgroup of patients majorly need of scratching (for example the patient with RIF) has to be identified. The procedure could increase the risk of latent infections and consequently it could determine sub-fertility. The best approach for scratching (hysteroscopy versus endometrial biopsy) has to be investigated. Further studies are necessaries to resolve these unanswered questions.

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Massive uterine adenomyosis: a long-term followup of its conservative surgical treatment

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ABSTRACT

Fifteen patients with massive diffuse adenomyosis underwent laparotomic uterine debulking. Retrospective analysis regarded menstrual characteristics, pelvic pain, dyspareunia and reproductive outcome. Statistical analysis was obtained using t test. P<0.05 was considered significant. Mean age was 34.6 years.
Follow-up lasted a mean of 41.4 months. No intraoperative nor postoperative complications occurred. At 12 months after surgery, 13 patients (87%) reported complete resolution of menorrhagia, mean VAS for dysmenorrhea was 1.8 ± 2.48 and mean VAS for chronic pelvic pain was 1.0 ± 2.17. At 6 months after surgery all patients had normal hemoglobin levels. One patient had 2 spontaneously-conceived term pregnancies. Despite the low postoperative pregnancy rate obtained in this study, symptoms were significantly improved in terms of dysmenorrhea, menorrhagia and sideropenic anemia. The long-term follow-up shows persistence of the improvement in symptoms.

Keywords: diffuse adenomyosis, conservative surgery, dysmenorrhea, menorrhagia.

SOMMARIO

Quindici pazienti con adenomiosi diffusa sono stati sottoposti a debulking uterino laparotomico. L'analisi retrospettiva ha osservato le caratteristiche mestruali, il dolore pelvico, la dispareunia e l'esito riproduttivo. L'analisi statistica è stata condotta utilizzando un t test. P<0.05 è stato considerato come significativo. L'età media dello studio è di 34.6 anni. Il follow-up è durato in media 41.4 mesi. Non si è verificata nessuna complicanza, né durante l'operazione né dopo.
A 13 mesi dall'operazione, 13 pazienti (87%) hanno riportato una completa risoluzione della menorragia. La media della VAS per la dismenorrea è stata di 1.8 ± 2.48 mentre la media della VAS per il dolore pelvico cronico è stata di 1.0 ± 2.17. A 6 mesi dall'operazione tutti i pazienti hanno riportato livelli di emoglobina regolari. Una paziente ha avuto 2 gravidanze spontanee a termine. Nonostante il basso tasso di gravidanza post-operatorio ottenuto in questo studio, i sintomi quali: la dismenorrea, la menorragia, e l'anemia sideropenica, sono migliorati significativamente. Il follow-up a lungo termine mostra un continuo miglioramento dei sintomi.

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INTRODUCTION

Uterine adenomyosis is a common benign gynecologic disorder which is commonly observed in women in their late 30s and 40s. Symptoms are nonspecific, can frequently be severe and include menorrhagia, dysmenorrhea, chronic pelvic pain and infertility[1]. While the focal subtype of adenomyosis is usually treated conservatively through resection of the nodules, hysterectomy is still considered the standard treatment for diffuse adenomyosis. In contrast with endometriosis[8,9], uterine adenomyosis is more frequently found in multiparous women, but it also affects nulligravid women. Treatment in the latter cases is therefore guided principally by the patient's desire to preserve the uterus and potential fertility and to avoid morbidity linked to hysterectomy. Management of diffuse disease is still lacking specific guidelines, due to the paucity of studies in the literature especially regarding its conservative treatment. The present study reports the long-term follow up of 15 patients who have undergone conservative surgical treatment for massive diffuse uterine adenomyosis.

MATERIALS AND METHODS

All fifteen patients with intraoperative and histological confirmation of massive diffuse adenomyosis involving at least two-thirds of the anterior and/or posterior uterine walls, who underwent laparotomic conservative uterine debulking by the same surgeon (L.F.) between November 2004 and April 2010 at the tertiary center of the Department of Obstetrics and Gynecology of our Institute, were retrospectively analysed regarding menstrual characteristics, pelvic pain, dyspareunia and reproductive outcome. Massive diffuse adenomyosis was defined at the preoperative workup as the presence of lesions involving at least two-thirds of the uterine body. Preoperative work-up included a complete blood panel, transvaginal and transabdominal pelvic ultrasound (US) and pelvic magnetic resonance imaging (MRI) (**fig.1**). Laparotomic uterine debulking involved resection of the area of myometrium affected by adenomyosis, judged by macroscopical visual inspection and palpation following myometrial incision of the diseased area suggested at the preoperative imaging workup.

Gonadotropin-releasing hormone agonists were not administered preoperatively in order to allow adequate intraoperative evaluation of the consistency and size of the adenomyotic mass.

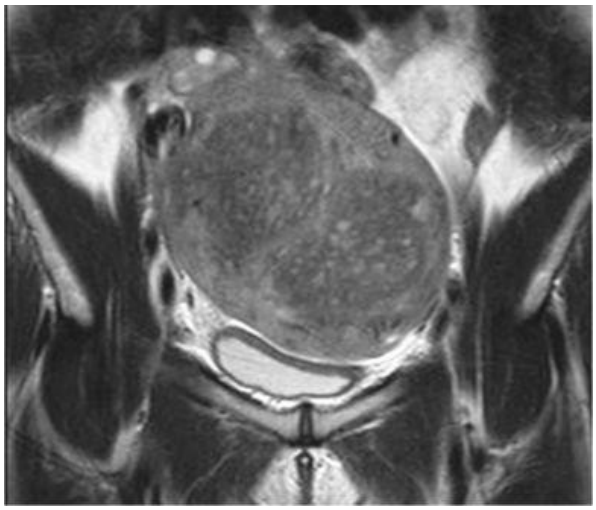

Figure 1.
T2-weighted fat-saturated MRI image showing transverse section of uterine myometrium subverted by diffuse adenomyosis.

Oral iron supplementation was prescribed with 329,7 mg ferrous sulphate and 4 micrograms folic acid for 4 months prior surgery and 1 month postsurgically. Surgery was performed through a suprapubic transverse laparotomic incision, followed by uterine mobilization and pelvic exploration. The uterus is kept lifted out of the abdomen during the surgical procedure. After inspection and palpation of the uterus body, a sagittal incision is made on the anterior and/or posterior walls so that the affected myometrium is exposed. The endometrial cavity is opened systematically in order to aid excision of the adenomyotic lesions while sparing the endometrium. Once the extent of the diseased myometrium has been assessed, a monopolar knife is used to excise the margins of the adenomyotic tissue (**fig.2**) while taking care to avoid damage to the Fallopian tubes.

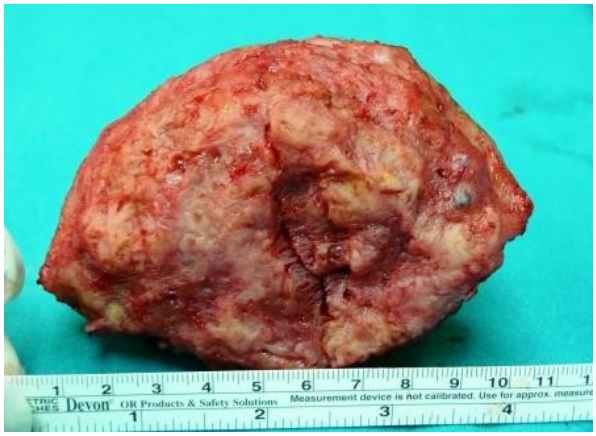

Figure 2.
Cuneiform section of myometrium affected by diffuse adenomyosis.

Resection was considered to be complete when at least two-third of the adenomyotic tissue had been removed while leaving enough myometrium to allow adequate myometrial reconstruction. The endometrial cavity is closed with interrupted sutures in 3-0 Vicryl. The myometrial defect is then sutured along two layers in 2-0 Vicryl, respectively a first deep interrupted sutures then followed by a superficial continuous suture which includes the serosa.

Follow up visits were programmed at 6, 12, 24 months and every year thereafter. Parameters that were evaluated at each follow up visit included a blood panel, a pelvic US scan and symptom analysis, i.e. dysmenorrhea, dyspareunia, pelvic pain and menstrual bleeding. Dysmenorrhea, dyspareunia and pelvic pain were analyzed using a Visual Analogue Scale (VAS)[2]. Statistical analysis was obtained using a t- test. $P < 0.05$ was considered significant. Menstrual bleeding was referred by the patients as mild, moderate or severe. Reproductive outcome was analyzed in those patients seeking a pregnancy.

The study was exempt from Institutional Review Board approval due to its retrospective nature of analysis of a conservative surgical treatment.

All women included in this study had signed an informed consent agreeing for their clinical data to be used anonymously for research purposes, along with the informed consent regarding the surgical procedure.

RESULTS

Mean patient age was 34.6 (26-41) years. Follow up lasted at least 19 months (mean 41.4 months; 19-38 months). All patients preoperatively reported moderate-severe dysmenorrhea with a mean VAS of 7.5 ± 1.46 ($P < 0.0001$). Six patients (40%) complained of deep dyspareunia, two of which mild and four moderate, with mean VAS of 2.1 ± 2.74 ($P < 0.04$). Eight of the 15 patients (47%) reported chronic pelvic pain, two of which mild and six of which severe, with mean VAS of 3.6 ± 3.85 ($P < 0.031$). The other seven patients complained of chronic pelvic pressure.

Four and 4 patients had respectively primary and secondary infertility. One patient had previously undergone surgery for diffuse adenomyosis. Menorrhagia was complained by all 15 patients. The mean preoperative hemoglobin levels showed sideropenic anemia in 13 of the 15 patients (87%), despite all had been taking oral iron supplements for 4 months prior to surgery; 7 and 6 of these had respectively moderate and mild anemia. In 5 patients the area of adenomyosis involved the posterior uterine wall, in 4 both the anterior and posterior walls, in another 4 the anterofundal portion of the uterus, and in 2 only the anterior wall. Surgery lasted a mean time of 108 minutes (89-145 minutes) and blood loss was a mean of 660 mL (50-2000 mL). None of the patients required blood transfusions and no major intra- nor postoperative complications occurred. Histopathological examination confirmed uterine adenomyosis in all 15 patients. (**Table 1**).

Table 1.
Table 1. Baseline characteristics of the cohort.

Characteristics	Number
Age (years)	34 (26-41)
Dysmenorrhea moderate-severe	15 ± 0
Deep Dyspareunia	6 (40%)
- Mild	2
- Severe	4
Chronic pelvic pain	8 (47%)
- Mild	2
- Severe	6
Infertility	
- Primary	4
- Secondary	4
Menorrhagia	15 ± 0
Preoperative sideropenic anemia	13 (87%)
- Mild	6
- Moderate	7
Site of uterine adenomyosis	
- Posterior wall	5
- Anterior e posterior wall	4
- Anterofundal wall	4
- Anterior wall	2

At 12 months after surgery, 13 patients (87%) reported complete resolution of menorrhagia, while 2 referred slight improvement, i.e. moderate menorrhagia. Postoperative data at 12-month follow up showed absence of dysmenorrhea in 9 cases (60%), mild and moderate dysmenorrhea in respectively 3 cases and moderate in another 3 (mean VAS 1.8 ± 2.48).

Of the 6 patients who preoperatively referred dyspareunia, 4 (67%) referred its complete remission and only 2 (33%) referred mild dyspareunia (mean VAS 0.4 ±1.06). Five of the eight patients (62.5%) who preoperatively complained of chronic pelvic pain referred

absence of pain since after surgery, 2 had moderate pain and 1 mild pain (mean VAS 1.0 ± 2.17). At respectively 6 and 12 months after surgery, all patients had normal hemoglobin levels. Mean age of the patients wishing to conceive was 37 years (30-44 years). Only one patient, who had primary infertility, had 2 spontaneously- conceived term pregnancies, which resulted in programmed caesarean sections. One other patient with primary infertility unsuccessfully attempted three intrauterine inseminations. One patient with secondary infertility also unsuccessfully underwent one cycle of in-vitro fertilization and embryotransfer (IVF- ET). Respectively two patients with primary infertility and two with secondary infertility are currently being evaluated at our Infertility Center. Four patients refer they will seek a pregnancy in the next future. (**Table 2**).

Table 2.
At 12 months after surgery.

Characteristics	Number
Absence of Dysmenorrhea	9 (60%)
Mild Dysmenorrhea	3
Moderate Dysmenorrhea	3
Absence of Dyspareunia	4 (67%) *
Mild Dyspareunia	2 (33%) *
Absence of Chronic pelvic pain	5 (62.5%)*
- Mild	1
- Moderate	2
Menorrhagia	13 (87%)
Postoperative sideropenic anemia	0
Mean age of the patients wishing to conceive	37 (30-44)

* four of the six that referred dyspareunia preoperatively
* five of the eight that referred chronic pelvic pain preoperatively

DISCUSSION

Surgical therapy in women with severe diffuse adenomyosis has been limited to hysterectomy for many years. With the continuous development in imaging methods, uterine adenomyosis not only is encountered more frequently, but may also be more accurately described in the growing number of nulliparous patients over 35 years of age seeking a pregnancy. Despite such growing diagnostic power, there are scanty reports in the scientific literature on the therapeutic options in women with diffuse symptomatic adenomyosis. Data is even scantier on the management of most severe, yet not uncommon, forms of massive diffuse involvement of the myometrium. Symptoms in these cases are often severe as well as refractory to the commonly recommended hormonal treatments. In infertile and/or symptomatic patients seeking a pregnancy, a diagnosis of diffuse adenomyosis may only temporarily benefit from medical therapy such as the levonorgestrel intrauterine device (Lng- IUD) or gonadotropin releasing hormones agonists, whereas the recommended surgical treatment, i.e. hysterectomy, cannot be considered a treatment option in these patients.

Among the conservative surgical treatments for uterine adenomyosis, new and less aggressive options have been introduced including endomyometrial ablation and uterine artery embolization. However, the scientific literature reports suboptimal efficacy of these methods, i.e. around 50% in the treatment of diffuse disease[3,4]. Also, most studies evaluating these methods lack histopathologic confirmation of diffuse adenomyosis and have a relatively short follow up, thus not allowing full assessment of the long-term benefits.

Above all, the number of cases of diffuse uterine adenomyosis are scanty and its myometrial extension superficially described nor stratified. While these minimally invasive techniques may be effective in the focal type of adenomyosis, accurate demarcation nor complete removal of diffuse lesions cannot be achieved. On the other hands laparotomy also enables palpation and identification of diseased tissue, easy hemostasis and assessment of the integrity of the endometrial cavity.

Similary to the only two reports in the literature that studied conservative treatment in cases with massive diffuse uterine adenomyosis, this study is flawed by its nonrandomized nor controlled design. In spite of these shortcomings, its methodology does show patient stratification, a long-term follow up and the presence of histopatological diagnosis, as well as uniformity of the type of adenomyosis. While in the by Osada and colleagues[5] 14 out of 26 (53,8%) patients obtained a term pregnancy, in our study post treatment pregnancy rates were low alike the study by Nishida et al.[6] (1 out of 44 cases). In our study, 4 (67%) of the six pregnancy-seeking patients were aged between 36-44 years, which may have influenced the obstetric outcome. Unlike our study, Nishida et al.[6] performed monolateral salpingectomy systematically in all patients as part of the surgical procedures.

The number of patients included in this

study is admittedly low, due to the stringent inclusion intraoperative criteria in which only cases of diffuse adenomyosis involving at least two-thirds of the anterior and/or posterior walls were included, thus yielding more specific data. Also other studies in literature presents a small number of patients. Despite the low postoperative pregnancy rate obtained in this study, symptoms were significantly improved in terms of dysmenorrhea, menorrhagia and sideropenic anemia. The long-term follow up also shows persistence of the improvement in symptoms, thus providing continuous relief in terms of quality of life of this patients.

Various medical and surgical methods have been developed for the management of a condition that until recently had hysterectomy as its only option. Data in the literature especially concerning conservative treatment for extensive diffuse uterine adenomyosis is extremely scanty, thus further research on these treatment methods is warranted[7]. This study shows that conservative treatment of massive diffuse adenomyosis can be considered a safe as well as effective procedure, with good results in terms of relief from severe dysmenorrhea, pelvic pain and menorrhagia.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no conflict of interests.

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Riassunto delle Caratteristiche del Prodotto

1. DENOMINAZIONE DEL MEDICINALE. MECLON "20% + 4% crema vaginale" MECLON "200 mg/10 ml + 1 g/130 ml soluzione vaginale". **2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA.** *Crema vaginale.* 100 g contengono: **Principi attivi:** Metronidazolo 20 g; Clotrimazolo 4 g. **Eccipienti:** contiene sodio metil p-idrossibenzoato e sodio propil p-idrossibenzoato. Per l'elenco completo degli eccipienti, vedere paragrafo 6.1. *Soluzione vaginale.* Flacone da 10 ml. 10 ml contengono: **Principio attivo:** Clotrimazolo 200 mg. Flacone da 130 ml. 130 ml contengono: **Principio attivo:** Metronidazolo 1 g. **Eccipienti:** contiene sodio metil p-idrossibenzoato e sodio propil p-idrossibenzoato. Per l'elenco completo degli eccipienti, vedere paragrafo 6.1. **3. FORMA FARMACEUTICA.** *Crema vaginale. Soluzione vaginale.* **4. INFORMAZIONI CLINICHE. 4.1 Indicazioni terapeutiche.** *Crema vaginale.* Cervico-vaginiti e vulvo-vaginiti causate da *Trichomonas vaginalis* anche se associato a *Candida albicans*, *Gardnerella vaginalis* ed altra flora batterica sensibile. MECLON crema vaginale può essere impiegato anche nel partner a scopo profilattico. *Soluzione vaginale.* Coadiuvante nella terapia di cervico-vaginiti, vulvo-vaginiti causate da *Trichomonas vaginalis* anche se associato a *Candida albicans*, *Gardnerella vaginalis* ed altra flora batterica sensibile. MECLON soluzione vaginale può essere impiegato anche dopo altra terapia topica od orale, allo scopo di ridurre il rischio di recidive. **4.2 Posologia e modo di somministrazione.** *Crema vaginale.* Somministrare profondamente in vagina il contenuto di un applicatore una volta al giorno per almeno sei giorni consecutivi, preferibilmente alla sera prima di coricarsi, oppure secondo prescrizione medica. Nelle trichomoniasi, maggior sicurezza di risultato terapeutico si verifica con il contemporaneo uso di Metronidazolo per via orale sia nella donna non gestante che nel partner maschile. Per un'ottimale somministrazione si consiglia una posizione supina, con le gambe leggermente piegate ad angolo. Per ottenere una migliore sterilizzazione è preferibile spalmare un po' di MECLON crema vaginale anche esternamente, a livello perivulvare e perianale. Se il medico prescrive il trattamento del partner a scopo profilattico, la crema deve essere applicata sul glande e sul prepuzio per almeno sei giorni. *Istruzioni per l'uso:* Dopo aver riempito di crema un applicatore, somministrare la crema in vagina mediante pressione sul pistone, fino a completo svuotamento. *Soluzione vaginale.* Somministrare la soluzione vaginale pronta una volta al giorno, preferibilmente al mattino, oppure secondo prescrizione medica.
Nella fase di attacco l'uso della soluzione vaginale deve essere associato ad adeguata terapia topica e/o orale. L'irrigazione va eseguita preferibilmente in posizione supina. Un lento svuotamento del flacone favorirà una più prolungata permanenza in vagina dei principi attivi e quindi una più efficace azione antimicrobica e detergente. *Istruzioni per l'uso:* Dopo aver versato il contenuto del flaconcino nel flacone, inserire la cannula vaginale sul collo del flacone stesso. Introdurre la cannula in vagina e somministrare l'intero contenuto. **4.3 Controindicazioni.** Ipersensibilità verso i principi attivi od uno qualsiasi degli eccipienti. **4.4 Avvertenze speciali e opportune precauzioni d'impiego.** Informi il paziente di evitare il contatto con gli occhi. L'impiego contemporaneo di Metronidazolo per via orale è soggetto alle controindicazioni, effetti collaterali ed avvertenze descritte per il prodotto summenzionato. Evitare il trattamento con Meclon durante il periodo mestruale. Con medicinali contenenti Metronidazolo per uso sistemico sono stati segnalati casi di epatotossicità severa/insufficienza epatica acuta, comprendenti casi con esito fatale, con esordio molto rapido dopo l'inizio del trattamento in pazienti affetti da sindrome di Cockayne. Pertanto, in questa popolazione Metronidazolo deve essere utilizzato dopo un'attenta valutazione del rapporto rischio-beneficio e solo in mancanza di trattamenti alternativi. Le analisi della funzionalità epatica devono essere effettuate appena prima dell'inizio della terapia, durante e dopo la fine del trattamento, fino a quando i parametri della funzionalità epatica non saranno rientrati nella norma o non saranno raggiunti i valori al basale. Se i valori delle analisi della funzionalità epatica dovessero aumentare notevolmente durante il trattamento, il farmaco deve essere interrotto. I pazienti affetti da sindrome di Cockayne devono essere avvisati della necessità di segnalare immediatamente al medico qualsiasi sintomo di potenziali lesioni epatiche e di interrompere il trattamento con Metronidazolo. **4.5 Interazioni con altri medicinali e altre forme di interazione.** Nessuna. **4.6 Gravidanza e allattamento.** In gravidanza il prodotto deve essere impiegato solo in caso di effettiva necessità e sotto il diretto controllo del medico. **4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari.** MECLON non altera la capacità di guidare veicoli o di usare macchinari. **4.8 Effetti indesiderati.** Dato lo scarso assorbimento per applicazione locale dei principi attivi Metronidazolo e Clotrimazolo, le reazioni avverse riscontrate con le formulazioni topiche sono limitate a: *Disturbi del sistema immunitario:* Non nota (la frequenza non può essere definita sulla base dei dati disponibili): reazioni di ipersensibilità. *Patologie della cute e del tessuto sottocutaneo:* Molto rari (frequenza <1/10.000): fenomeni irritativi locali quale prurito, dermatite allergica da contatto, eruzioni cutanee. L'eventuale manifestarsi di effetti indesiderati comporta l'interruzione del trattamento. **4.9 Sovradosaggio.** Non sono stati descritti sintomi di sovradosaggio. **5. PROPRIETÀ FARMACOLOGICHE. 5.1 Proprietà farmacodinamiche.** Categoria farmacoterapeutica: Antinfettivi ed antisettici ginecologici/ Associazioni di derivati imidazolici - Codice ATC: G01AF20. Meccanismo d'azione/effetti farmacodinamici: Il MECLON è una associazione tra Metronidazolo (M) e Clotrimazolo (C). Il (M) è un derivato nitroimidazolico ad ampio spettro di azione antiprotozoaria e antimicrobica. Ha effetto trichomonicida diretto ed è attivo su cocchi Gram-positivi anaerobi, bacilli sporigeni, anaerobi Gram-negativi. Presenta attività spiccata sulla *Gardnerella vaginalis.* Non è attivo sulla flora acidofila vaginale. Il (C) è un imidazolico con spettro antifungino molto ampio (*Candida*, etc.). È attivo anche su *Trichomonas vaginalis*, cocchi Gram-positivi, Toxoplasmi, etc. È stato documentato che l'associazione Clotrimazolo-Metronidazolo dà luogo ad effetti di tipo additivo, pertanto essa è in grado di conseguire tre vantaggi terapeutici principali: 1) Ampliamento dello spettro d'azione antimicrobica, per sommazione degli effetti dei due principi attivi; 2) Potenziamento dell'attività antimicotica, antiprotozoaria ed antibatterica; 3) Abolizione o ritardo della comparsa dei fenomeni di resistenza. Studi microbiologici in vitro hanno dimostrato che l'attività trichomonicida e antimicotica risulta potenziata quando il (M) e il (C) sono associati nelle stesse proporzioni che sono presenti nel MECLON. Anche l'attività antibatterica esaminata su diversi ceppi di microorganismi è risultata elevata ed è emerso un potenziamento di essa quando i due principi attivi del MECLON vengono associati. **5.2 Proprietà farmacocinetiche.** Dalle indagini farmacocinetiche sui conigli, cani e ratti risulta che dopo ripetute applicazioni topiche di MECLON non si rilevano concentrazioni apprezzabili di Clotrimazolo e Metronidazolo nel sangue. Per applicazione vaginale nella donna il (M) e il (C) vengono assorbiti in una percentuale che varia tra il 10% e il 20% circa. **5.3 Dati preclinici di sicurezza**. La tossicità acuta del MECLON nel topo e nel ratto (os) è risultata molto bassa, con una mortalità di appena il 20% dopo 7 giorni, a dosi molto elevate (600 mg/Kg di (C) e 3.000 mg/Kg di (M), sia da soli che associati). Nelle prove di tossicità subacuta (30 giorni) il MECLON, somministrato per via locale (genitale) nel cane e nel coniglio, non ha determinato alcun tipo di lesione nè locale nè sistemica anche per dosi molte volte superiori a quelle comunemente impiegate in terapia umana (3-10 Dtd nel cane e 100-200 Dtd nel coniglio; 1 Dtd = dose terapeutica/die per l'uomo = ca. 3,33 mg/Kg di (C) e ca. 16,66 mg/Kg di (M)). Il MECLON somministrato durante il periodo di gravidanza per via topica vaginale nel coniglio e nel ratto non ha fatto evidenziare alcun segno di sofferenza fetale per dosi die di 100 Dtd, nè influssi negativi sullo stato gestazionale. **6. INFORMAZIONI FARMACEUTICHE. 6.1 Elenco degli eccipienti**: *Crema vaginale.* **Eccipienti:** Stearato di glicole e polietilenglicole; Paraffina liquida; Sodio metile p-idrossibenzoato; Sodio propile p-idrossibenzoato; Acqua depurata. *Soluzione vaginale.* Flacone da 10 ml. **Eccipienti:** Alcool ricinoleilico; Etanolo; Acqua depurata. Flacone da 130 ml. **Eccipienti:** Sodio metile p-idrossibenzoato; Sodio propile p-idrossibenzoato; Acqua depurata. **6.2 Incompatibilità.** Non sono note incompatibilità con altri farmaci. **6.3 Periodo di validità.** *Crema vaginale:* 3 anni. *Soluzione vaginale:* 3 anni. **6.4 Precauzioni particolari per la conservazione.** Questo medicinale non richiede alcuna particolare condizione per la conservazione. **6.5 Natura e contenuto del contenitore.** MECLON *crema vaginale.* Tubo in alluminio verniciato internamente con resine epossidiche e fenoliche. Gli applicatori monouso sono di polietilene. Tubo da 30 g + 6 applicatori monouso MECLON *soluzione vaginale.* Flaconi di polietilene a bassa densità; flaconcini di polietilene; cannule vaginali di polietilene. 5 flaconi da 10 ml + 5 flaconi da 130 ml + 5 cannule vaginali monouso. **6.6 Precauzioni particolari per lo smaltimento e la manipolazione.** Nessuna istruzione particolare. **7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO.** Alfasigma S.p.A. - Viale Sarca, n. 223 - 20126 Milano (MI). **8. NUMERI DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO.** MECLON *crema vaginale*: A.I.C. n. 023703046. MECLON *soluzione vaginale*: A.I.C. n. 023703059. **9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE.** 16.01.1979 / 01.06.2010.
10. DATA DI REVISIONE DEL TESTO. Agosto 2017.

Medicinale non soggetto a prescrizione medica (SOP). CLASSE C.

meclon
Metronidazolo, Clotrimazolo

1. DENOMINAZIONE DEL MEDICINALE. MECLON "100 mg + 500 mg ovuli". **2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA.** Un *ovulo* da 2,4 g contiene: **Principi attivi:** Metronidazolo 500 mg; Clotrimazolo 100 mg. Per l'elenco completo degli eccipienti, vedere paragrafo 6.1. **3. FORMA FARMACEUTICA.** *Ovuli.* **4. INFORMAZIONI CLINICHE. 4.1 Indicazioni terapeutiche.** Cerviciti, cervico-vaginiti, vaginiti e vulvo-vaginiti da *Trichomonas vaginalis* anche se associato a *Candida* o con componente batterica. **4.2 Posologia e modo di somministrazione.** Lo schema terapeutico ottimale risulta il seguente: 1 ovulo di MECLON in vagina, 1 volta al dì. **4.3 Controindicazioni.** Ipersensibilità verso i principi attivi od uno qualsiasi degli eccipienti. **4.4 Avvertenze speciali e opportune precauzioni d'impiego.** Informi il paziente di evitare il contatto con gli occhi. L'impiego contemporaneo di Metronidazolo per via orale è soggetto alle controindicazioni, effetti collaterali ed avvertenze descritte per il prodotto summenzionato. Evitare il trattamento con Meclon durante il periodo mestruale. MECLON ovuli va impiegato nella prima infanzia sotto il diretto controllo del medico e solo nei casi di effettiva necessità. Con medicinali contenenti Metronidazolo per uso sistemico sono stati segnalati casi di epatotossicità severa/insufficienza epatica acuta, comprendenti casi con esito fatale, con esordio molto rapido dopo l'inizio del trattamento in pazienti affetti da sindrome di Cockayne. Pertanto, in questa popolazione metronidazolo deve essere utilizzato dopo un'attenta valutazione del rapporto rischio-beneficio e solo in mancanza di trattamenti alternativi. 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È attivo anche su *Trichomonas vaginalis*, cocchi Gram-positivi, Toxoplasmi, etc. È stato documentato che l'associazione Clotrimazolo-Metronidazolo dà luogo ad effetti di tipo additivo, pertanto essa è in grado di conseguire tre vantaggi terapeutici principali: 1) Ampliamento dello spettro d'azione antimicrobica, per sommazione degli effetti dei due principi attivi; 2) Potenziamento dell'attività antimicotica, antiprotozoaria ed antibatterica; 3) Abolizione o ritardo della comparsa dei fenomeni di resistenza. Studi microbiologici in vitro hanno dimostrato che l'attività trichomonicida e antimicotica risulta potenziata quando il (M) e il (C) sono associati nelle stesse proporzioni che sono presenti nel MECLON. Anche l'attività antibatterica esaminata su diversi ceppi di microorganismi è risultata elevata ed è emerso un potenziamento di essa quando i due principi attivi del MECLON vengono associati. **5.2 Proprietà farmacocinetiche.** Dalle indagini farmacocinetiche sui conigli, cani e ratti risulta che dopo ripetute applicazioni topiche di MECLON non si rilevano concentrazioni apprezzabili di Clotrimazolo e Metronidazolo nel sangue. Per applicazione vaginale nella donna il (M) e il (C) vengono assorbiti in una percentuale che varia tra il 10% e il 20% circa. **5.3 Dati preclinici di sicurezza.** La tossicità acuta del MECLON nel topo e nel ratto (os) è risultata molto bassa, con una mortalità di appena il 20% dopo 7 giorni, a dosi molto elevate (600 mg/Kg di (C) e 3.000 mg/Kg di (M), sia da soli che associati). Nelle prove di tossicità subacuta (30 giorni) il MECLON, somministrato per via locale (genitale) nel cane e nel coniglio, non ha determinato alcun tipo di lesione nè locale nè sistemica anche per dosi molte volte superiori a quelle comunemente impiegate in terapia umana (3-10 Dtd nel cane e 100-200 Dtd nel coniglio; 1 Dtd = dose terapeutica/die per l'uomo = ca. 3,33 mg/Kg di (C) e ca. 16,66 mg/Kg di (M)). Il MECLON somministrato durante il periodo di gravidanza per via topica vaginale nel coniglio e nel ratto non ha fatto evidenziare alcun segno di sofferenza fetale per dosi die di 100 Dtd, nè influssi negativi sullo stato gestazionale. **6. INFORMAZIONI FARMACEUTICHE. 6.1 Elenco degli eccipienti. Eccipienti:** Miscela idrofila di mono, di, tri-gliceridi di acidi grassi saturi. **6.2 Incompatibilità.** Non sono note incompatibilità con altri farmaci. **6.3 Periodo di validità.** 3 anni. **6.4 Precauzioni particolari per la conservazione.** Questo medicinale non richiede alcuna particolare condizione per la conservazione. **6.5 Natura e contenuto del contenitore.** 10 ovuli in valve in PVC, racchiusi in scatola di cartone. **6.6 Precauzioni particolari per lo smaltimento e la manipolazione.** Nessuna istruzione particolare. **7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO.** Alfasigma S.p.A.- Viale Sarca, n. 223 - 20126 Milano (MI). **8. NUMERO DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO.** A.I.C. n. 023703010. **9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE.** 16.01.1979 / 01.06.2010. **10. DATA DI REVISIONE DEL TESTO.** Agosto 2017.

Medicinale non soggetto a prescrizione medica (SOP). CLASSE C.