

Management of infertility in women with endometriosis

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Abstract

Although there is confirmed an association between endometriosis and infertility, precise standards of managements have not yet been established. Ablation of endometriotic lesions plus adhesiolysis in minimal to mild endometriosis is more effective than diagnostic laparoscopy alone in improving fertility. Suppression of ovarian function and hormonal treatment alone are not effective in improving fertility. In women with stage I/II endometriosis associated infertility, expectant management or IUI after laparoscopy can be considered for younger patients. Women 35 years of age or older should be treated with IUI or IVF-ET. IVF pregnancy rate are lower in women with endometriosis than in those with tubal infertility. For women with stage III/IV endometriosis who fail to conceive following conservative surgery IVF-ET is should be offered.

INTRODUCTION

It is estimated that endometriosis occurs in about 10% of women at reproductive age, in Poland according to Starczewski *et al.* (2009) in 7–15% of women, from which 50% coexists with infertility. Despite the numerous studies it is difficult to prove a direct causal relationship between them, except cases complicated with the presence of adhesions and ambilateral oviducts occlusion. Numerous data in turn, demonstrate their obvious significant connection. That opinion is supported with statistical data pointing that endometriosis is considerably more often diagnosed in women with infertility when compared to fertile women (Kaminski *et al.* 2006; Bokor *et al.* 2010). It is estimated that it is diagnosed 10 times more often during the laparoscopy. Also, the results of numerous scientific studies demonstrate that rela-

tionship. The attention is paid more often on the necessity of collection and statistical elaboration of the data enabling an introduction of corrections to endometriosis classification proposed by the American Fertility Society (AFS), and then after the change of the name on the American Society for Reproductive Medicine (ASRM), slightly complemented (ASRM 1997). The above activities would be aimed at even more detailed assessment of disease severity in an aspect of treatment undertaken (Roberts & Rock 2003).

FACTORS INFLUENCING FERTILITY DECREASE IN WOMEN WITH ENDOMETRIOSIS

Anatomical and functional changes in oviducts are a factor which evidently causes infertility. They may proceed in a form of complete occlusion of

both oviducts, decrease in fimbriae motility, oviducts impairments constricting transport, and peritubal adhesions preventing ovum trapping. Such changes are observed the most often in a severe and moderate form. The next factor decreasing the chances of getting pregnant is intercourse avoiding caused by pain accompanying endometriosis. Numerous studies were devoted to significance of immunological factors acting at the stage of fetus implantation in uterus, increased local estradiol production and decreased those of progesterone (Kitawaki *et al.* 1997; Roberts & Rock 2003; Mikołajczyk *et al.* 2009). In etiology, an attention is paid to a significance of intraperitoneal fluid and the presence in it of pro-inflammatory factors promoting implantation, proliferation and further development of ectopic endometrial tissue (Tamaya *et al.* 1979). Cytokines contained in the fluid may, by an influence on expression of cell membrane receptors, unprofitably affect spermatozoa motility (Barcz *et al.* 2000), spermatozoa capacitation and ovum fertilization (Iborra *et al.* 2005). The special attention is paid to ovaries dysfunction. As was demonstrated, one of the reasons may be an increased expression of progesterone receptors A (PR-A) and estrogen α (ER- α) in granule cells in women with IV class endometriosis according to AFS when compared to women without endometriosis and with oviductal factor of infertility (Iborra *et al.* 2005). There are some studies pointing reasons of infertility in disturbed excretion of hormones leading in a consequence to improper development of ovarian follicles and ovulation. Attention was paid to an occurrence of luteinized unruptured follicle syndrome and luteal insufficiency. Lowered estradiol concentration and elevated prolactin concentration is observed in women with infertility and endometriosis, when compared to healthy women, while gonadotropic hormones concentrations do not differ (Karita *et al.* 2011). Destruction of ovarian tissue caused by the presence of ovarian cyst or surgical treatment may cause both decrease in functional volume of ovarian tissue, and decrease in a number of follicles what may result in ovarian reserve decrease. The frequency of postoperative impairments of the ovary is determined as 13% (Cunha-Filho *et al.* 2001). In older women, a decrease in ovarian reserve combined with poorer cells quality points the necessity of infertility therapy intensification. Ovary functions seem to be dependent also on endometriosis process severity (Iborra *et al.* 2005). It is also significant whether the process concerns one or both ovaries. However, endometrioid cysts are unilateral the most often (72–81% of cases) (Benaglia *et al.* 2010). The presence of endometriosis foci within the body of uterus is very unprofitable phenomenon from infertility point of view. It results in a disorders syndrome including constant local production of estradiol and prostaglandins, myometrium impairment, sustained uterine contraction activity, resistance on progesterone and in a consequence lack of, or improper trophoblast implantation.

ENDOMETRIOSIS DIAGNOSIS

Endometriosis may occur in various forms and therefore the reliable diagnosis may be made only during laparotomy or laparoscopy based on macroscopic assessment of lesions and histopathological examination of segments where the presence of glandular tissue and endometrial stroma is observed. Recently, the opinion that macroscopic determination of the presence of foci characteristic for endometriosis if sufficient for diagnosis is more popular one. Not always however, their presence is of a clinical significance. The foci of endometriosis may constitute an intermediate stage in the process of cytotoxicity and lesions removing, what happens in women with proper immunological reaction or, like in case of immunological tolerance, the lesions may develop and transform in moderate and severe form (Vercellini *et al.* 1998). A useful method for recognition of endometrial cysts and adenomyosis is ultrasonography. It does not however allows for visualization of fine surface foci (Vercellini *et al.* 1992). Currently, the possibility of an application of an assessment of chemokines, low-molecular proteins formed by immunological system cells, and their receptors expression in diagnostics is the subject of the studies (Moore *et al.* 2002). In a differential diagnostics, the significant meaning is also attributed to the method of magnetic resonance – especially useful in differentiation of endometrial and dermoidal cysts, which may sometimes give very similar images in an ultrasonographical examination. That method also finds an application in case of presence of endometriosis foci in rectovaginal fascia.

PROGNOSTIC FACTORS OF INFERTILITY TREATMENT IN WOMEN WITH ENDOMETRIOSIS

Treatment of infertility in women with endometriosis must have an individual course. The selection of therapy method should be preformed after basic diagnostic examinations according to recommendations of Polish Association of Reproduction Medicine (<http://rozdrodczosc.pl>). The special attention should be paid to an assessment of ovarian reserve, which may be lowered especially in women after surgical treatment of ovarian cyst and in older women. The recognition of predictably unprofitable factors, including long time of infertility lasting (above 3 years), age of the woman above 35 years, and presence of male factor, allows in many cases for an application of such a method, which in a given couple provides the biggest chances of giving birth. However recommendations concerning the treatment of pain connected to endometriosis are elaborated, it is difficult to determine strict schemes of proceeding in the case of infertility. That results from the incapability to conduct randomized control clinical examinations, comparing an effectiveness of various treatment methods. Selection of infertility treatment method is usually

based on own experiences and on retrospective studies published in that range.

The proceeding in the case of endometriosis diagnosis in women who do not plan to get pregnant currently.

Endometriosis is sometimes diagnosed in women during laparoscopy performed from reasons other than infertility (Agic *et al.* 2007). It is believed, that women with diagnosed presence of single endometriosis foci on the peritoneum but without clinical symptoms (pain) do not require any treatment. The above opinion is justified by the observations, that these are often multiparas and many of them get pregnant in a natural way. In healthy women the changes are removed as a result of efficiently functioning immunological system (Vercellini *et al.* 1992). However, not always happens so. Immunological disorders may lead to an intensification of changes and conversion to more severe form (Missmer *et al.* 2004). As may be concluded from that, the predicting about further natural course of endometriosis is often difficult. In such cases, the decision as regards further proceeding should be based on an assessment of degree of endometriosis severity according to AFS and the presence of clinical symptoms, and aim at maintenance of fertility and decrease in infertility risk in further age. It is assessed, that changes removal decreases a risk of recurrence. Some authors point the advantages resulting from an application of progestagens or hormonal contraceptive preparations (Vercellini *et al.* 2008; Seracchioli *et al.* 2009; Dovey & Sanfilippo 2010). Usually, the treatment lasts long time, and thus it is the most profitable to administer preparations containing progestagens lack of androgenic activity.

EXPECTANT MANAGEMENT

It is estimated that about 10–25% of women with endometriosis get pregnant spontaneously (Vercellini *et al.* 1997). No statistically significant differences in percentage of pregnancies depending on the degree of clinical severity according to AFS classification were observed. Worse results were however obtained in the group of women with IV class, but the differences were not significant (Guzick *et al.* 1997). The examination points the role of immunological disorders in infertility etiology in women with endometriosis. From the above reasons, when no unprofitable prognostic factors are observed and the risk of recurrence is small, the expectant management may be recommended. During that time, the observation of cycles with ovulation control is recommended. Also the monitoring of process development is an important issue. The attention should be paid to pain complaints. Their occurrence or intensification may demonstrate the disease progress. The ultrasonographic examination may be useful only in the case of cystous lesions presence. However, the monitoring of Ca125 antigen which concentration increases with endometriosis severity seems to be a valuable issue (Kraśnicki 2001; Bal *et al.* 2008).

SURGICAL TREATMENT IN INFERTILITY ASPECT

The characteristic feature of conducted currently surgical procedures in women with endometriosis is the fact, that they are performed using little invasive technique with an attention paid to possibly the smallest tissues damage and in possibly the most saving manner, so that to increase rather, not decrease the chances on fertility. All treatments, when it is possible technically and no contraindications exist, are performed in laparoscopic way. Some authors point the benefits resulting from removing of disease foci during the laparoscopy (Vercellini *et al.* 1997). That not only concerns classical techniques, such as ovarian cystectomy, bipolar coagulation of surface peritoneum lesions, but also deep lesions excision, adhesions removing. Such procedures, except pain removing, may appear to be effective also in the case of infertility – both as regards spontaneous pregnancy and improved results of successive pharmacological treatment (Chapron *et al.* 1999; Werbrouck *et al.* 2006; Barri *et al.* 2010). Also the kind of treatment conducted is significant. An excision of endometrial cyst of a diameter above 4 cm improves the fertility and decreases chances of endometriosis recurrence when compared to puncture, drainage, capsule coagulation (Beretta *et al.* 1998). There is lack of randomized control studies estimating an effectiveness of surgical treatment of III and IV class endometriosis according to AFS, and it is not known whether surgical excision of lesions increases fertility in such advanced disease process (Kennedy *et al.* 2005). While deciding about the surgical treatment, the risk and benefits resulting from instrumental treatment should be always assessed. Based on published results of the study it seems that in the case of infertility, surgical treatment provides fewer benefits than expected previously. It may however improve anatomical conditions, but also lower ovarian reserve (Nowroozi *et al.* 1987). It also does not improve bimolecular disorders playing an important role in etiopathogenesis of infertility in women with endometriosis.

PHARMACOLOGICAL TREATMENT

Numerous papers may be found in the literature devoted to an effectiveness of pain treatment and significance of therapies in lowering of development of endometriosis severity and decreasing the risk of recurrences; however, there is a lack of reliable papers pointing an effectiveness of pharmacological treatment in case of infertility. The results of the study demonstrate, that pharmacotherapy in a temperate and moderate form does not lead to increased chances of pregnancy obtaining in a natural way in women with infertility (Hull *et al.* 1987; Bayer *et al.* 1988). In women with endometriosis the fertility cannot be improved using pharmacological methods. In these women, the techniques of assisted reproduction should be used.

COMBINED SURGICAL AND PHARMACOLOGICAL TREATMENT

The purpose of postoperative pharmacological treatment is to eliminate remaining foci using different hormonal medicines. It lasts the most often for a period of 3–6 months. There are no papers so far estimating an effectiveness of such a procedure, and both when regards the kind of medicines used, and also successive proceedings – expectant management, insemination, *in vitro* fertilization. The combined therapy is assessed well – hormonal treatment with successive surgical treatment (Donnez *et al.* 1987). It is not important, which of hormonal preparations used in endometriosis treatment is applied. One of the papers describes the results of pentoxifylline application – the medicine from immunomodulators group, inhibiting formation of free oxygen species and lowering the level of tumor necrosis factor (TNF), directly after laparoscopy to women with asymptomatic minimal and moderate endometriosis for 12 months. The percentage of pregnancies in the group treated with pentoxifylline was 31%, and in placebo group it was 18.5%, however the differences were not significant statistically (Balasch *et al.* 1997).

INTRAUTERINE INSEMINATIONS

The intrauterine inseminations may be performed in the case of presence of at least one unobstructed oviduct and lack of male infertility factor. Usually, in temperate and moderate form up to 6 inseminations are preformed. In women with small degree of endometriosis severity, the results of insemination are similar like obtained in women with idiopathic infertility factor, and after insemination with donor semen. Slightly better results are obtained in stimulated cycles (Matorras *et al.* 2002). It was observed, that the percentage of pregnancies for a cycle after ovulation stimulation with clomiphene citrate or gonadotropins and 4 intrauterine inseminations in women with minimal and temperate endometriosis performed directly after laparoscopic foci removing, and idiopathic infertility, did not differ significantly and was 21%, 18.9% and 20.5%, respectively (Werbrouck *et al.* 2006). Similarly, the results of insemination with donor semen (azoospermia in the partner) performed in women with minimal endometriosis and without endometriosis did not differ significantly and were 8.6% and 13.3% per cycle, respectively (Matorras *et al.* 2010).

ASSISTED REPRODUCTION TECHNIQUES

The assisted reproduction techniques include the following methods: *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), embryo replacement (ER). The procedures may proceed within the programs of semen and oocytes donation. In some women they are the only, and in other the ultimate treatment

manner. They are performed in case of presence of oviductal and male factor, or when other methods appeared to be ineffective. Their application depends on age of the woman, period of infertility lasting, endometriosis degree, inclusion of ovaries and oviducts into the process, therapy led so far and pain occurrence. Attention should also be paid to treatment costs and an attitude to the therapy led. However, some authors point that endometriosis impairs the results of treatment with assisted reproduction techniques, and it is not known whether surgical treatment increases an effectiveness of their successive application (Marcoux *et al.* 1997; Shahine *et al.* 2009), but higher pregnancy percentages are obtained as a result of *in vitro* fertilization techniques (Barri *et al.* 2010). It was noted moreover, that an application of gonadoliberin analogue for 3–6 months, and hormonal contraceptive preparations for 6–8 weeks, improves an effectiveness of *in vitro* fertilization (de Ziegler *et al.* 2010). The meta-analysis of studies comparing an effectiveness of treatment with IVF method depending on infertility reasons was conducted. It demonstrated significantly lower index in women with endometriosis (index of chances 0.56; 95% confidence interval, 0.44–0.70) when compared to women with oviductal infertility factor (Barnhart *et al.* 2002). That is explained by worse quality of oviducts and foetuses. The results of the study are however not unequivocal. In one of the studies, in a group of 81 women with unilateral endometrial ovarian cysts subjected to IVF procedure, no differences in a number of ova obtained during puncture were noted (Almog *et al.* 2011). Women with endometriosis exhibit also worse ovarian response and need higher gonadotropins doses in *in vitro* fertilization programs; however the percentage of implantations is not decreased. It is believed moreover, that in women with moderate and severe form, the elongated administration (3–6 months) of gonadoliberin analogue would be considered, since such a therapy improves treatment results. Despite numerous critical remarks against an application of *in vitro* fertilization in infertile women with endometriosis, it should be emphasized, that an effectiveness of any other kind of treatment has not been proved so far (Holoch & Lessey 2010). It is maybe also worth to emphasize, that no significant differences were observed in frequency of endometriosis recurrences in women with endometriosis diagnosed during laparoscopy and treated with gonadotropins in IVF programs (20.6% of recurrences) when compared to women, who after laparoscopy were not treated (37.9% of recurrences) (Coccia *et al.* 2010). Similar percentage of recurrences (22%) was obtained by other authors (Benaglia *et al.* 2010).

SUMMARY

Despite that about 10–25% of women with diagnosed endometriosis get pregnant spontaneously, there is a relationship between that disease and infertility. The

proceeding in case of coexistence of infertility and endometriosis should be dependent on the degree of disease severity, form, clinical symptoms, age of woman, length of infertility period and other factors significant from therapy point of view. In women who currently do not plan pregnancy, the hormonal treatment should be considered, having in mind lowering of the risk of disease development and/or its recurrence, and increase in chances of getting pregnant in older age. In women with infertility coexisting with endometriosis it is difficult to establish proceeding standards, including surgical and pharmacological ones, due to problems enabling randomization of the study and proper selection of examined groups. The results of the studies (non control ones) point benefits resulting from ectopic foci removing in all degrees of endometriosis severity, both when regards natural pregnancy and an application of insemination and *in vitro* fertilization methods. The infertility in women with endometriosis cannot be cured using pharmacological methods. In women below 35 year of life with temperate and moderate severity degree, at least one oviduct patent, and with lack of male factor, the expectant attitude may be accepted or an application of intrauterine inseminations in cycles with ovulation stimulation may be used. Women above 35 year of life should be treated using inseminations or *in vitro* fertilization methods. IVF-ET/ICSI are often not only ultimate, but also the only methods leading to giving birth. Their application should be considered in each woman with endometriosis (Szamatowicz 2007).

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