Patient Information: Endometriosis—Disease Process and Treatment

Endometrium is the medical term for the tissue that lines the inside of the uterus, the tissue that in a normally menstruating woman builds up and breaks down every month. The “breaking down” or shedding of the endometrial tissue is what a woman recognizes as her menstrual period every month.

The term endometriosis, a disease of the female pelvic organs, is derived from the word endometrium. In the disease state endometriosis, normal endometrium lining tissue is found in abnormal anatomic locations. Normally the endometrium grows only in the inside of the uterus, but in a woman with endometriosis endometrial tissue is found in other locations, most commonly in or next to the ovaries, or between the uterus and rectum, or between the uterus and bladder. Occasionally women with endometriosis will have endometrial tissue in anatomic locations even more distant from the uterus than this. How the normal endometrial tissue comes to grow in abnormal anatomic locations is something that will be discussed a bit further below.

Endometriosis is probably the most controversial, most debated, and most poorly understood disease in all of reproductive medicine. There is still much debate as to what causes endometriosis, what symptoms it causes and how it causes them, and how extensive the disease must be before it becomes plausible and likely that the disease will cause symptoms. These debates about the nature of endometriosis can be frustrating for the patient—every different source of information she consults may give a different picture of the disease! These controversies not withstanding, I will proceed now with what I feel are the best and most accurate explanations of how endometriosis causes infertility and how our treatment options combat the infertility caused by endometriosis.
Over the years, studies of endometriosis have produced a number of unexpected and paradoxical findings. As regards endometriosis and infertility treatment, the most important and reasonably consistently demonstrated paradox is this: Treatment that reliably eradicates the anatomic areas of endometriosis does not nearly as reliably eradicate, i.e. cure, the infertility caused by or associated with the endometriosis. Any theory of how endometriosis causes infertility must explain this great paradox.

Treatments that reasonably effectively, i.e. in 75-95% of cases, eradicate the anatomic spots of endometriosis have been available for decades. Currently, four classes of such eradicative treatments, one surgical and three non-surgical, are in common use. With surgical treatment, the areas of endometriosis are identified and excised or destroyed, with destruction typically achieved by burning with electrical or laser cautery. The effectiveness of surgical treatment is probably best and most accurately characterized by a widely praised study that was published in 1997 in the *New England Journal of Medicine*. In that study several hundred women with endometriosis and infertility underwent surgery. In approximately half the study subjects the endometriosis was surgically destroyed, and in the other half the presence of endometriosis was confirmed at surgery, but the endometriosis areas left untreated. In the six months following surgery, 31% of the women whose endometriosis was destroyed conceived, while 18% of the women whose endometriosis was untreated conceived during the same time interval. It is probably fair to estimate that in the year following surgery, 40-45% of the treated women conceived, while 25-30% of the untreated women conceived. While it is somewhat encouraging that 40-45% of treated women conceive within a year after surgery, it is somewhat discouraging to note that treatment benefit is only 15-20% (40-45% minus the conception rate in the control group, 25-30%), because 25-30% of the women would presumably have gotten pregnant even if they had not undergone the expense, discomfort, and risks of surgery. This study also illustrates the importance in any study of endometriosis and infertility of having an untreated control group, because a certain percentage of patients with endometriosis will conceive even if they receive no treatment whatsoever.
The other three types of traditional eradicative endometriosis treatment are non-surgical, *i.e.* pharmacological. The three types of medications all work to wither away the endometriosis by modifying the woman’s hormonal status. GnRH analogues, the most commonly used of which is Lupron, work by lowering estrogen levels to the menopausal range. Progesterone formulations, such as Prometrium, Provera, and birth control pills act by intensifying progesterone and in some cases by also lowering estrogen. Androgenic agents, *i.e.* Danazol, work by modestly increasing the levels of male hormone. All three medications, like surgery, eradicate the areas of endometriosis in 75-95% of appropriately chosen patients, but also like surgery have infertility cure rates much lower than their disease eradication rates. Based on the clinical evidence that does exist, which admittedly is not extensive, probably most fertility specialists believe that medical treatment is less effective than surgery in curing endometriosis associated infertility.

Again, the great paradox of endometriosis-associated infertility is that treatment that reliably eradicates the anatomic areas of endometriosis does not nearly as reliably eradicate, *i.e.* cure, the infertility caused by the endometriosis. What follows is the best and most plausible explanation that can be given for this paradox. It is likely that most women with endometriosis have a significant amount of reverse menstruation. When they menstruate they not only bleed vaginally, they also bleed “backwards,” with blood and fragments of endometrial tissue passing backwards out the fallopian tubes and into the lower abdominal cavity. Indeed, it is the implantation and growth of backwards passed endometrial tissue that very likely account for the presence of the spots of endometriosis in the first place. Thus, women with endometriosis basically have a load of blood and menstrual debris dumped into their abdominal cavities with every menstrual period. The body seems to react to this load of menstrual blood very much like it would react to a large bruise on the arm or leg. An inflammatory response is generated that brings about the slow, steady digestion and resorption of the blood, like the slow healing and fading of a bruise. A large number of studies measuring the intensity of the inflammatory response in the lower abdominal cavity/pelvis have been performed, and these studies are virtually unanimous in showing an increased level of inflammation in
women with endometriosis, even women with only mild endometriosis, compared to women without endometriosis. Furthermore, the increased level of inflammation likely is an important culprit in causing the infertility associated with the endometriosis. Increased levels of inflammatory enzymes and increased levels of activity of inflammatory white cells may cause damage to the sperm, the egg, the newly formed fertilized egg, or the chemicals necessary for sperm and egg communication and transport, thereby preventing pregnancy from occurring. The concept of reverse menstruation leading to chronic pelvic inflammation is the logical explanation for the great paradox of endometriosis. We can destroy the spots of endometriosis with surgery or with hormonal medications, but the process of reverse menstruation leading to chronic inflammation continues on, and this chronic inflammation continues to suppress the chances of successfully achieving a pregnancy.

The concept of chronic reverse menstruation leading to an environment of chronic inflammation in the female pelvis also helps to explain the rationality and efficacy of other endometriosis treatment modalities that have become increasingly utilized over the last ten years. One popular modality is “maximum non-surgical fertility enhancement treatment,” or superovulation insemination, where the woman is given powerful fertility drugs and artificially inseminated (by the technique of intrauterine insemination). The fertility drugs serve several purposes--they can bring about the maturation and release of more eggs than would occur otherwise, and they generally make the ovaries larger, thereby bringing them closer to the fallopian tubes, where the eggs need to go after they are released. Artificial insemination greatly increases the number of sperm that make it to the upper regions of the pelvis. With these techniques, the female pelvis is “flooded” with more eggs and sperm than would occur otherwise, thereby improving the chances that egg and sperm will survive, escape the inflammatory environment of the pelvis, and go on to interact successfully to produce a pregnancy.

The concept of chronic reverse menstruation leading to an environment of chronic inflammation also explains why in vitro fertilization-embryo transfer (IVF-ET) would be an appropriate therapeutic intervention for endometriosis. In IVF-ET, the development of multiple eggs is stimulated with fertility drugs as with superovulation/insemination. In IVF-ET, though, the eggs are surgically removed (via aspiration through a needle) from
the woman’s ovaries before they are released. The eggs are then inseminated, fertilized, and incubated in the “safe haven” of the laboratory, where they stay for several days before being inserted through a catheter into the woman’s uterus. IVF-ET is the most complete bypass of the inflammatory environment of the pelvis of all the therapeutic modalities, and indeed has the highest pregnancy rate per cycle of treatment (albeit at the highest cost per cycle of treatment). The success per cycle of IVF-ET treatment is the same for women with endometriosis as it is for the other common major causes of infertility such as tubal blockage and male factor infertility (low sperm count). This implies that the fundamental mechanisms involved in egg maturation and development, fertilization, and embryo implantation and development are not inherently flawed in women with endometriosis. Moreover, it is consistent with the concept that an inflammatory pelvic environment that interferes with egg and sperm transport and survival is the main barrier to pregnancy in women with endometriosis.

There is one other intervention that is performed commonly in the course of infertility evaluation and treatment that may impact pregnancy rates in women with endometriosis—the hysterosalpingogram. The hysterosalpingogram is a standard infertility diagnostic test done to evaluate the anatomy of a woman’s uterus and fallopian tubes. It does not detect the presence of endometriosis, but it does detect the presence of certain other common and important diseases affecting fertility. In the hysterosalpingogram procedure x-ray “dye” is injected into the patient’s cervix and passes upward into the uterus and fallopian tubes. The flow of the dye is visualized via x-ray. If the fallopian tubes are open, the dye drips out the fallopian tubes and pools in the abdominal cavity.

Although the hysterosalpingogram is considered to be primarily a diagnostic test, it likely carries therapeutic benefit also. It has long been observed that the pregnancy rate in infertile couples seems to increase during the six to twelve months following the hysterosalpingogram procedure. It has generally been thought that the mechanism of the hysterosalpingogram’s fertility enhancing effect is a cleansing effect on the fallopian tubes. The thought has been that the procedure washes mucus and debris out of the fallopian tubes and thereby opens them. However, there is some evidence that there may be other factors at work. For decades two different types of x-ray dye have been used for
hysterosalpingography, water-based and oil-based. The post-procedure pregnancy rates of the two dyes have recently been studied. In a study of several hundred general infertility patients, \textit{i.e.} patients who may have had a number of different underlying diseases causing their infertility, patients were randomly assigned to have either oil-based or water-based dye for their hysterosalpingograms. In the nine months following the procedure, 33\% of the oil-based dye group became pregnant, compared to only 17\% of the water-based dye group, a difference which statistical analysis showed was significant, not due merely to chance. To the best of my knowledge a study comparing oil dye and water dye in a patient population comprised exclusively of women with endometriosis has not been performed. However, there is no good reason to believe that oil dye would not have a similar beneficial effect in women with endometriosis. If anything, one might expect that the oil dye would be especially beneficial for fertility enhancement in women with endometriosis, because there is some evidence that oil dye can suppress the activity of the white blood cells that mediate inflammation that reside in the pelvic/lower abdominal cavity. Thus, though classified as a diagnostic test, for the reasons described above the hysterosalpingogram, especially a hysterosalpingogram with oil-based dye, might be considered a therapy for endometriosis.

In summary, in this communication we have described current thought regarding how endometriosis causes infertility, and we have described seven different therapies that are used in the treatment of endometriosis associated infertility. We have mentioned that the “popularity” of the various treatments has varied over the years, and that currently some treatments are more “popular” than others. To reiterate, the seven therapies are:

1) Surgical destruction
2) GnRH analogues (\textit{e.g.} Lupron)
3) Progesterone formulations—Provera, Prometrium, and birth control pills
4) Danazol
5) Superovulation (treatment with “fertility drugs”) and intrauterine insemination
6) In vitro fertilization-embryo transfer (IVF-ET)
7) Hysterosalpingogram, possibly with oil-based dye (not historically categorized as specific treatment for endometriosis)

Hopefully, the description of these therapies, and the discussion of how they may work to
overcome the barrier to pregnancy that endometriosis poses will help you to make the best and most informed treatment decisions possible.

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