Endometriosis: Peer-Reviewed Analysis

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Endometriosis

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Definition

Endometriosis is a disease in which tissue similar to the inner lining of the uterus, called the endometrium, is present in locations in the body outside of the uterus. The misplaced tissue may be on the ovaries, the surface of the uterus, fallopian tubes, intestines, bladder, bowel, or peritoneum (the thin lining of the abdominal cavity). Occasionally endometrium is present in even more distant sites outside of the abdomen, like, for example, the lung or a limb. Endometriosis is a dynamic disease with periods of development, progression, and even regression.

Women with endometriosis may experience a variety of symptoms, though endometriosis can also be asymptomatic. Lower abdominal pain is most common, and pain can be particularly intense before and during menstrual periods, as well as during ovulation. Some women have pain throughout the menstrual cycle. Infertility, pain with intercourse, fatigue, allergic diseases, and bowel and bladder problems are also common with endometriosis (Olive and Schwartz 1993).

Epidemiology of Endometriosis

Because endometriosis is difficult to diagnose with certainty without surgery, the prevalence of the disease in the general population is uncertain. Sometimes the diagnosis becomes apparent during surgery that is being done because of abdominal pain or for some other unrelated purpose. Sometimes the diagnosis is suspected and laparoscopy, through a “belly button” incision, is done to further investigate. The diagnosis of endometriosis is often delayed or missed because of myths and taboos surrounding menstruation and sex. Many women and girls are told that their pain is imagined or normal (Ballweg 1998).

Estimates of the prevalence of endometriosis range from 2-4% of all women and girls to 10-15% of all women in their reproductive years (Eskenazi and Warner 1997). Endometriosis is present in as many as 30-50% of women with infertility and 69% of teenagers with chronic pelvic pain not responsive to anti-inflammatory medication or birth control pills (Cramer and Missmer 2002; Laufer et al 1997). An early age of onset of menstruation and shorter menstrual cycles appear to slightly increase the risk of developing endometriosis.

It has been suggested that endometriosis is more common now than it once was, but this trend is difficult to confirm because of inconsistent record keeping and new technologies that permit more accurate diagnosis.

Causes

The cause of endometriosis is still unknown. It is generally accepted, however, that endometriosis is the result of a complex series of events that may link genetic susceptibility with environmental factors. The immune and endocrine (hormone) systems are directly involved in the development of endometriosis (Oral and Arici 1997). When the lining of the uterus, the endometrium, is shed during normal menstruation, most of the bloody tissue is discharged through the cervix into the vagina. Several theories attempt to explain the development of endometriosis.

One step that many researchers believe necessary for endometriosis to develop is some degree of backward, or retrograde, flow of endometrial tissue up the Fallopian tubes and into the abdominal cavity. However, since more than 90% of women experience retrograde menstruation, other factors are almost certain to play a role as well Moreover, retrograde menstruation does not explain the presence of endometriosis in parts of the body outside of the abdomen.

Another theory holds that endometriosis develops through the transformation of cells lining the peritoneal cavity (coelomic metaplasia). This theory is based on the observation that endometrial and peritoneal cells come from the same precursor cells during fetal development. Yet another theory suggests that endometrium from the uterus is spread through the blood vessels, lymphatics, or during surgery to abnormal locations.

Regardless of which theory is correct, additional steps that ensure the survival of endometrial tissue outside of the uterus are also necessary. The degree to which endometrium misplaced outside of the uterus becomes established depends on several factors, including preparation of the implantation site. Studies show that displaced endometrial tissue secretes enzymes and various growth factors that aid its survival and promote implantation. Hormones, especially estrogen, aid this process. Enzyme, growth factor, and hormone levels are under both genetic and environmental control.

Survival of misplaced endometrial tissue also appears to depend on failure of the immune system to scavenge or “clean up” endometrial implants (Lebovic et al 2001; Sidell et al 2002). In some women endometrial cells have a prolonged survival when they occur in abnormal locations (Meresman et al 2000). Immune system malfunction is also the result of genetic and environmental factors (Osteen and Sierra-Rivera 1997), and may help explain why women with endometriosis are at increased risk of cancer of the ovary, breast, melanoma and non-Hodgkins lymphoma (Brinton et al 1997; Hornstein et al 1997). In fact, many researchers see similarities

between the growth of misplaced endometrial tissue and the growth of cancer cells. Although endometriosis is not itself considered a form of cancer, some of the features that allow misplaced endometrium to grow and develop resemble those of cancer. Women with endometriosis also have an increased likelihood of having other conditions involving immune system malfunction, including allergies, eczema, and food sensitivities (Lamb and Nichols 1986; Nichols et al 1987; Sinaii et al in press).

Various studies have attempted to identify risk factors for endometriosis, but their results are often conflicting, perhaps because of limitations of study design. In general, the risk of endometriosis appears to increase with shorter cycle length, longer duration of menstrual flow, and reduced number of pregnancies. Some studies suggest a decreased risk with heavy smoking and increased exercise, each of which is associated with decreased estrogen levels.

In summary, endometriosis develops when endometrial-like tissue successfully implants and grows outside of the uterus. The process apparently results from a mixture of mechanical, hormonal, and immune system factors under the control of genetic and environmental influences.

Genetic Factors

The tendency to develop endometriosis appears to be influenced to some degree by genetic factors. Studies suggest that several different genes, each playing some role, are likely to be involved (Simpson et al 1980). Close relatives to someone with endometriosis have about a 5-8% increased risk of developing the condition when compared to the general population (Simpson and Bischoff 2000). An identical twin has an even larger risk (Zeyneloglu et al 1997; Foster and Agarwal 2002).

Environmental Factors

Dioxins and polychlorinated biphenyls (PCBs): Dioxins and furans are unintended by-products of waste combustion and other industrial processes. Municipal and medical waste incinerators, secondary copper smelters, cement kilns, polyvinyl chloride manufacture, and pulp and paper bleaching are among the leading sources of these and related chemical compounds. PCBs were intentionally produced in the US and around the world for decades for use in electrical equipment, paints, and lubricants. Although PCB manufacture was banned in the US in 1977, most of the PCBs ever produced are still present not only in older electrical equipment, but also in soil, sediments, and landfills. Dioxins, furans, and PCBs persist for years in the environment. They are also fat-soluble and their concentrations increase as they move up the food chain. Meat, dairy products, processed food, and fish contaminated with dioxin, furans, and PCBs are the principal sources of human exposure.

Dioxins, furans, and dioxin-like PCBs have a wide range of health effects in laboratory animals and humans, often at extremely low levels of exposure. These chemicals alter the levels and function of many different hormones, enzymes, and growth factors (Birnbaum 1994). Prenatal

exposures at very low levels are particularly toxic to the developing immune, reproductive, and hormone systems (Birnbaum and Cummings 2002).

The role of dioxins, furans, and dioxin-like polychlorinated biphenyls (PCBs) in the development of endometriosis has received considerable attention ever since a report of a high incidence of the disease in a colony of Rhesus monkeys that had been fed a diet containing small amounts (5 and 25 parts per trillion) of dioxin (Rier et al 1993). Examination of the monkeys ten years after dioxin exposure was discontinued showed that 70% of the animals receiving the low dose and more than 80% of the high dose animals had endometriosis, compared to 33% of control animals that had not been fed dioxin. The severity of endometriosis was also directly related to the degree of dioxin exposure. A follow-up study of these animals thirteen years after termination of dioxin exposure showed that endometriosis was more severe in those animals with higher exposure to dioxin-like PCBs as well (Rier et al 2001) . Though the animals were not purposely fed PCBs, the most likely source of their exposure was from contaminated feed, similar to the source for humans. The authors note that these impacts in monkeys may be relevant to humans, since the blood levels of dioxins and PCBs in the animals are similar to those in the blood and tissues of humans.

These findings triggered additional animal studies. In another species of monkey, dioxin increased the survival and growth of endometrium that was surgically implanted into the abdominal cavity (Yang et al 2000). Similarly, researchers studied the impact of dioxin exposure on the survival and growth of endometrial implants in rodents (Cummings et al 1996). Treatment with a low dose of dioxin before surgery, at the time of surgery, and several weeks following surgery caused an increase in the size and survival of the endometrial implants in the animals. These studies have been repeated with variations in the experimental protocol, showing that the impact of dioxin depends on the timing of exposure, the size of the dose, and other hormonal factors (Birnbaum and Cummings 2002).

This evidence in two species of monkeys and in rats and mice supports a relationship between exposure to dioxin or dioxin-like compounds and endometriosis. The evidence from human studies is somewhat limited and less clear.

One study in Israel reported a much higher proportion of women with surgically confirmed endometriosis to have detectable dioxin in their blood than women without endometriosis (Mayani et al 1997). In another study, researchers found no relationship between total PCBs and endometriosis (Lebel et al 1998). This second study is of limited value since all PCBs were measured rather than just dioxin-like PCBs or dioxin. All animal studies indicate that it is the dioxin-like qualities that seem to be related to endometriosis for this group of compounds, and only some, but not all, PCBs have dioxin-like toxicity. In Seveso Italy, a group of women exposed to the highest levels of the most toxic form of dioxin released in an industrial accident in the 1970s have recently been reported to have a doubled risk for endometriosis, but the increase

was not statistically significant (Eskenazi et al 2002). This study is limited by a small number of cases of endometriosis.

Other environmental chemicals: Since estrogen appears to be necessary for the growth and development of endometriosis, researchers have studied the impact in laboratory animals of other chemicals that have estrogen-like characteristics. Methoxychlor, a pesticide widely used in the US, including on the food supply, is weakly estrogenic and aids the growth of surgically-produced endometriosis in rodents (Cummings and Metcalf 1995). Another industrial compound, chlorodiphenyl ether, has a similar effect (Foster et al 1997).

These observations raise questions about the role of other commonly encountered industrial chemicals with estrogenic properties in the development or severity of endometriosis. Although most of these chemicals are weakly estrogenic when compared to naturally occurring estrogen, combined they may have a significant impact, particularly in susceptible individuals. Commonly encountered weakly estrogenic chemicals include bisphenol A (used in polycarbonate plastics, food and drink containers, dental sealants, glues and resins), some alkylphenols (used in detergents and some plastics), some pesticides (e.g. endosulfan as well as methoxychlor, used on the food supply), some phthalates (used in cosmetics, food containers, food wraps, and many other consumer products), among others.

Radiation: In the 1970s, because of an interest in the potential health effects of radiation on astronauts during space travel, the US government sponsored a study in which a colony of Rhesus monkeys was exposed to radiation of various kinds. Although the doses of radiation used were considerably higher than those experienced by the general public, including the exposure experienced during airplane travel, the risk of developing endometriosis was dramatically increased in the irradiated animals when compared to controls (Fanton and Golden 1991). The increases in endometriosis were pronounced, even in the lowest dose groups, and no threshold value has ever been established. The authors of the study concluded that "women receiving whole-body, or in particular, abdominal, exposure to penetrating doses of protons or X-rays should possibly be considered to be at higher risk of developing endometriosis than unexposed women."

One possible explanation for this effect of radiation is interference with normal immune system function. Normally, various components of the immune system are responsible for removing misplaced tissue cells that are growing inappropriately. Radiation can interfere with that process, by altering the expression of genes and allowing these cells to continue to grow (Palumbo et al 2001). This immune system impact may also help explain the increased risk of some cancers in women with endometriosis.

Summary

Endometriosis is a disease in which tissue similar to the lining of the uterus, the endometrium, implants and grows outside of the uterus, often in the abdominal cavity, frequently causing pain,

infertility, pain with sex, and bowel or bladder problems. Endometriosis requires involvement of hormones and immune system malfunction in order to develop, and is associated with increased risk of other immune system disorders and certain cancers. Although genetic factors may contribute to the risk of endometriosis in some women, human and animal studies indicate a potentially important role for environmental factors as well, including exposure to dioxins, furans, PCBs, chemicals that mimic estrogen, and radiation. It is important to consider that combinations of chemical and radiation exposures may add up to increase the risk more than would be expected from any one alone.

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