

The Estrogen Connection

Estrogen is the hormone--the chemical messenger--that turns a girl's body into a woman's body at puberty. Actually, there is a whole class of similar steroids, estrogens, which can stimulate the growth of the breasts and other female tissues. The most abundant and important estrogen secreted by a woman's ovaries is called **estradiol**. Estradiol is so potent that its concentration in a woman's blood is measured in **parts per trillion!** There is even some estradiol--about a tenth as much--made in a man's body, and both men and women need some estradiol for normal growth and maintenance of the bones.

After puberty, the levels of estrogen rise and fall twice with each menstrual cycle. Under the influence of the pituitary gland's **follicle stimulating hormone (FSH)**, new, egg-containing follicles develop in the ovaries during the first half (called the **follicular phase**) of the menstrual cycle. The follicular, estradiol-secreting cells surrounding the eggs proliferate, and so the ovaries secrete ever larger quantities of estradiol, reaching a peak about one day before ovulation. This **pre-ovulatory peak** is the highest blood level of estradiol a woman ever normally experiences in the non-pregnant state. It stimulates her pituitary gland to secrete another hormone, **luteinizing hormone (LH)**, which actually triggers ovulation.

After ovulation, the follicle which has expelled the egg becomes filled with another kind of cell called a **luteal cell**. These luteal cells proliferate under the influence of pituitary LH, thus secreting ever larger quantities of both estradiol and the pregnancy hormone **progesterone**, from which estradiol is made.

Since pituitary secretion of LH falls off quite sharply after ovulation, the **corpus luteum** (as the former follicle is now called) begins to regress about a week after ovulation, unless fertilization of the egg (**conception**) has taken place. If conception has occurred, the embryo begins--almost immediately--to secrete another chemical messenger, **human chorionic gonadotropin (HCG)***, which acts like LH to "rescue" the corpus luteum. If conception has not taken place, the corpus luteum essentially dies. Since luteal estrogen and progesterone are needed for (respectively) the growth and maturation of the **endometrium** (the uterine lining in which the embryo implants), the endometrium is shed as the menstrual flow or **menses**.

If, however, conception has occurred and the corpus luteum has been rescued, it proceeds to generate enormous concentrations of progesterone (necessary to permit implantation of the embryo and maintenance of the pregnancy) and estradiol. Significantly elevated levels (compared to non-pregnant levels at the same time of the menstrual cycle) of estradiol can be detected as early as 5 days after conception³⁶. As shown in **Figure 1**, by 7 to 8 weeks gestation (after the last menstrual period, or LMP), a pregnant woman's blood already contains six times more (i.e., 500% more) estradiol than it did at the time of conception, more than twice the highest level attained in the non-pregnant state (preovulatory peak).³⁷

In marked contrast, pregnancies destined to abort spontaneously (i.e., end in miscarriage) during the first trimester usually do not generate estradiol in quantities exceeding non-pregnant levels^{37,38} (**Figure 1**). One team of Swiss obstetricians, as far back as 1976, was actually able to predict spontaneous abortions with 92% accuracy with just a single measurement of estradiol!³⁸ Theoretically, this makes perfect sense: The very reason for the abortion is an inadequate supply of progesterone from which estradiol is made.

How estradiol, or estrogens in general, relate to breast cancer risk, has to do with their role in the growth of breast tissue. It is estradiol which makes the breasts grow to mature size at puberty, and which makes them grow again during pregnancy (at least the first two trimesters). The cells in the breast which are responsive to estradiol are those which are primitive, or **undifferentiated**. Once **terminally differentiated** into milk-producing cells, something which happens under the influence of other (still largely unknown) factors, breast cells can no longer be stimulated to reproduce.

It is the undifferentiated cells, which are also vulnerable to the effects of carcinogens (radiation, certain chemicals, etc.), which can give rise to cancerous tumors later in life. If a woman therefore has gone through some weeks of a normal pregnancy, and then aborts that pregnancy, she is left with more of these cancer-vulnerable cells than she had in her breasts before she was pregnant. In addition, any abnormal, potentially cancer-forming cells already in her breasts (and such cells are present to some extent in all people) have also been stimulated to multiply. All this translates into a statistically greater probability that a cancerous tumor may eventually arise.

In contrast, a full term pregnancy results in full differentiation of the breast tissue for the purpose of milk production, which leaves fewer cancer-vulnerable cells in the breasts than were there before the pregnancy began. This translates into the well known breast cancer risk lowering effect of a full term pregnancy.

It is also widely accepted (although not universally observed) that women who start having children at a younger age lower their risk of getting breast cancer later in life³⁹. Presumably, this is because the sooner the breasts become fully mature for the purpose milk production, the less likely is the presence of abnormal, potentially cancer-forming cells, from accumulated carcinogenic insults (and what these are is still largely unknown). In support of this theory, an experimental study of the effect of nulliparity (i.e., not having any babies) and induced abortion in increasing breast cancer incidence in young rats treated with chemical carcinogens was published as far back as 1980⁴⁰. (Interestingly, the data and conclusions of this research are still positively acknowledged even by those who disparage the ABC link².) More recently, the same research team has also published an excellent study of the differentiation in human breast tissue as a function of pregnancy and age.⁴¹

In addition, since there are always some undifferentiated cells (and even some abnormal cells) in a woman's breasts, overexposure to the growth promoting effects of estradiol or other estrogens, whenever the exposure takes place, contributes to breast cancer risk.

Not surprisingly, then, most known risk factors for breast cancer are characterized by some form of estrogen overexposure. For example, women who attain puberty at an early age, or who enter the menopause at a late age, or who have fewer or no children, are exposed to more surges of estradiol that come with more menstrual cycles. Women who breast feed their children also experience fewer menstrual cycles, thereby helping to lower their risk.

Even risk factors which are unrelated to reproduction seem to operate via an estrogen-mediated mechanism. For example, post-menopausal obesity increases risk, presumably because adipose (fat) cells actually synthesize estrogens, thus raising an obese woman's blood estrogen levels. Even in the dietary realm, it is known that chronic alcohol consumption raises blood estrogen levels, and it also appears to raise breast cancer risk. Likewise for a diet high in animal fat, compared to a vegetarian diet. Conversely, certain vegetables known to help protect against cancer, such as members of the broccoli and cabbage family, help a woman's body to eliminate estrogens more rapidly.

Since the effect of estrogens on breast cancer risk has been well recognized for many years, doctors have been wary of prescribing such medications as post-menopausal estrogen replacement therapy for older women, especially those with any family history of breast cancer. As it turns out, epidemiological studies do not even find a consistent trend of increasing risk among such women, probably because the dosage is much lower than the estrogen levels naturally produced by pre-menopausal ovaries.

One would think, therefore, that doctors would have been concerned about possible increases in breast cancer risk attributable to induced abortion, even in the absence of epidemiological data, given the extremely high estradiol levels experienced by women even in the first several weeks of normal pregnancy.

Then again, epidemiological data has hardly been lacking. As early as 1957, a large study of Japanese women⁴² evidenced a significantly increased breast cancer risk among women who had had any induced--but not spontaneous--abortions. To date, 30 separate studies of induced abortion have been published worldwide, with 24 showing increased risk. In contrast, over 30 studies involving only or mostly spontaneous abortions fail to show any significant trend¹.

Finally, there is one additional and crucial aspect of spontaneous abortion vis-a-vis breast cancer risk that must be noted, namely the effect of post-first trimester miscarriages. Most miscarriages occur in the first trimester, and over 90% of these are characterized by abnormally low maternal estradiol levels³⁸. However, there is reason to believe that pregnancies which survive the first trimester (and they couldn't survive without adequately high progesterone levels, which are paralleled by estradiol) **are** likely to raise breast cancer risk, as induced abortions do.

Theoretically, a miscarriage due to physical trauma or anatomic defect (e.g. "lazy cervix") is essentially an unintended induced abortion, with the same hormonal changes associated with an elective induced abortion.

Although epidemiological evidence of this is very scanty, prudence would suggest a heightened vigilance for breast cancer among such women and their doctors.-JB-

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