Clinical Tests of Estrogen Injections on Women with Abnormal Menstrual Cycles During the Early 1920s by Jean Paul Pratt and Edgar Allen

In the early twentieth century US, Jean Paul Pratt and Edgar Allen showed that if doctors injected estrogen into women with abnormal menstrual cycles, the cycles would become more normal. During clinical tests, researchers injected the hormone estrogen into patients who had menstrual ailments, which ranged from irregular cycles to natural menopause. The hormone estrogen functions in the menstrual cycle by signaling the tissue lining the uterus (endometrium) to thicken in preparation for possible pregnancy. In their clinical tests, Pratt and Allen showed that estrogen injected into female human subjects restored their normal menstrual cycle, removed symptoms such as hot flashes, and caused uterine tissue to thicken. The clinical tests conducted by Pratt and Allen provided experimental evidence and justification for the injection of isolated estrogen in women to alleviate, for a short amount of time, some menstrual ailments, and it contributed to later hormone therapy research.

During the 1920s, Pratt practiced gynecology and obstetrics at the Henry Ford Hospital in Detroit, Michigan. As a gynecologist and obstetrician, Pratt helped women maintain the health of their reproductive systems and deliver infants. Allen worked at the University of Missouri School of Medicine in Columbia, Missouri, as a professor of anatomy and researcher. Allen made possible the clinical tests of injectable estrogen when he developed a method in 1923, alongside researcher and Nobel Prize recipient Edward Adelbert Doisy, to separate estrogen from ovarian tissue. Allen and Doisy successfully located the main estrogen production center in women, isolated a pure sample of estrogen, and showed its effects in test animals. Allen's experiments after the isolation of estrogen showed that injecting estrogen in female mice caused their reproductive cycles to start and uterine tissues to grow. By injecting women who had menstrual ailments with estrogen, Pratt and Allen anticipated that they could restore the normal monthly cycles absent in some women, reduce symptoms such as hot flashes, and cause the uterine lining to thicken.

However, before Pratt and Allen tested estrogen injections in human subjects, Allen completed preliminary experiments on female rhesus macaque monkeys (Macaca mulatta). Allen chose to study macaques, which are non-human primates, because they have genetics and menstrual cycles similar to humans. Allen completed the preliminary tests to determine whether estrogen induced the same effects in primates as it did in mice and in other small mammals. Because the reproductive cycle differs across species, testing estrogen injections in species closely related to humans ensured the safety of the injection for human experimentation.

The reproductive estrous cycle that occurs in almost all mammals is different from the menstrual cycle that occurs in humans and in non-human primates such as monkeys. In both the estrous cycle and the menstrual cycle, the tissue layer lining the uterus thickens in preparation for possible egg implantation. If a fertilized egg does not implant in the thickened tissue, the tissue is shed from the walls of the uterus. The estrous cycle of most mammals differs from the menstrual cycle of primates in that the uterus reabsorbs the tissue lining if egg implantation does not occur. In comparison, the uterine tissue shed during the menstrual cycle is lost out of the vagina, causing visible menstrual bleeding in primates. Another difference between the menstrual cycle and the estrous cycle is that in the estrous cycle female animals are only sexually active during their estrus phase, often called heat, while during the menstrual cycle females can be sexually active anytime. Allen tested the effects of estrogen on the menstrual cycle in monkeys to see if similar results transpired compared

to the estrous cycle experiments in mice.

The results of Allen's preliminary experiments on monkeys mimicked those of his experiments on mice. When researchers removed the ovaries of monkeys, their menstrual bleeding and the redness that accompanied their external genitalia or labia went away. As Allen hypothesized, the ovaries produced estrogen, and without an estrogen production center, the lining of the uterus was shed and blood flow decreased to the labia.

In another experiment, Allen administered daily injections of estrogen into monkeys who had their ovaries previously removed to eliminate estrogen production. Allen noted that the redness of the monkeys' external genitalia resurfaced and that their uterine tissue began to thicken again, just as it did during the normal cycle before the researchers had removed the ovaries. Those experiments showed that the menstrual cycle in primates had similar if not identical reactions when doses of estrogen were administered as compared to his earlier tests on the estrous cycle in mice. Building on Allen's preliminary experiments in mice and monkeys, Allen and Pratt began testing estrogen injections in humans.

Pratt and Allen conducted their research to help women who frequently came into clinics and reported menstrual problems. They hypothesized that the menstrual ailments arose from a lack of estrogen. The researchers sought to test whether or not administering estrogen restored normal menstrual function in women who lacked the means to naturally produce estrogen at necessary levels to sustain a menstrual cycle. There were four groups of women in the study: those who previously had their ovaries removed and their uteruses remained intact, a condition called artificial menopause; those who had naturally ceased menstrual flow, a condition called menopause; those who were over twenty-years-old without having a single menstrual period, a condition called primary amenorrhea; and those who had an irregular amount of bleeding or bled on an irregular interval, a condition called scanty menstruation.

Pratt and Allen chose to exclude one part of Allen's previous experiments from the design of their clinical tests due to ethical concerns. The excluded part was about whether human sexual maturation could be brought on by estrogen injections. The result of Allen's sexual maturation test in young mice revealed that injections of estrogen reduced the amount of time for the onset of puberty and the first estrous cycles in mice. During the tests, three-week-old female mice matured in three to four days, approximately thirty days in advance of normal development. Allen had concluded from his experiment that estrogen functioned during puberty and during the estrous cycle, and that injecting estrogen into young female mice sped up their maturation. Allen and Pratt did not conduct those tests in humans, as they concluded it would be unethical to do so in young female children.

Pratt and Allen customized the procedures for each of the menstrual ailments under treatment. The tests lasted for various lengths of time to determine the effect of estrogen with short doses and long doses. The variation in testing also resulted from dealing with human subjects, as human subjects can withdraw from clinical trials or stop coming to sessions if they choose.

To test the effect of estrogen on artificial menopause, Allen and Pratt gave women with artificial menopause, who had previously had their ovaries removed, a constant dose of estrogen each morning and night for two to three weeks. The researchers injected the women with a dosage between 0.5 to 3 rat units of estrogen. One rat unit is equivalent to the minimum amount of estrogen needed to induce estrous in a rat, two rat units represents double the amount, and so on. The dosage value differed from patient to patient to determine the smallest amount of estrogen needed to produce a menstrual cycle in humans.

In all of the women in the group, Allen and Pratt conducted pelvic exams and saw that the women's uteruses enlarged after several days of injections. The change seen in the uteruses accompanied a change in the color of the cervix due to an increase in blood flow, a normal occurrence during the reproductive cycle. The patients noted that they felt their uteruses getting heavier and that they felt an increase in pressure on their pelvises. Allen and Pratt noted that this test did not exactly test for a menstrual ailment, as those patients no longer had ovaries and the ability to menstruate, but instead served as a control, paralleling their studies on spayed mice that had their ovaries removed. The results of estrogen injections in humans with removed ovaries matched the results of spayed

mice. In both tests the uterine tissue thickened. The women who received the estrogen injections experienced a cycle similar to the natural menstrual cycle, but lacked menstrual bleeding.

The next treatment group included women with natural menopause who were no longer having menstrual periods. As with their procedure for women with artificial menopause, Allan and Pratt injected women with natural menopause with 0.5 to 3 rat units of estrogen. Allen and Pratt noted that the injections of estrogen removed the patient's hot flashes and the feeling of nervousness across most of the patients. The researchers also noted that only a small amount of estrogen was needed to reduce the symptoms of menopause felt by those patients.

Pratt and Allen then tested the third group of patients with primary amenorrhea, who were over the age of twenty without having menstruated. Those patients received an estrogen injection dose from 15 to 90 rat units. The patients received injections for varying lengths of time, from two weeks to two months, given one to three times a day. Allen and Pratt varied the amount of estrogen given to determine the lowest possible amount needed to produce menstruation. Allen and Pratt said that the results of that experiment were difficult to assess as the patient's underdeveloped reproductive organs made pelvic examinations difficult. The patients receiving high doses of estrogen showed a small amount of tissue thickening in their uteruses but no signs of menstruation after they stopped getting estrogen injections.

The final group consisted of patients with scanty menstruation, either irregular in their amount of flow or their interval of menstruation, and who were all between the ages of twenty and thirty years old. Pratt and Allen gave patients one injection of estrogen a day for five consecutive days. After they stopped injecting the women, the patients experienced a typical menstrual flow. Allen and Pratt, after the first set of injections, administered estrogen in scheduled intervals to match a natural cycle. The administered cycle lasted somewhere around twenty-three days. The researchers waited twelve days after the initial flow, and then they began another set of injections lasting eleven days for each patient. After discontinuation of the injections, the patients' menstrual flows returned and increased slightly from the first set of injections. The researchers again discontinued the estrogen injections for twelve more days and started again until the researchers recorded menstrual flow. Allen and Pratt concluded that they had induced normal menstrual flow in women with abnormal menstrual cycles by injecting estrogen on a schedule that mimicked the natural cycle.

The results of Allen and Pratt's clinical tests matched the animal experiments, showing that estrogen injections had similar effects on species with different reproductive cycles. Pratt and Allen's clinical tests added information to the early study of hormone therapies involving estrogen, showing the potential for estrogen to restore menstrual flow and patterns in women with menstrual ailments.

Early clinical studies in the 1920s that involved estrogen injections portrayed quick and safe results for women suffering from menstrual ailments. However as time passed, hormone therapy patients reportered higher than normal rates of cancer. In 2001, researchers reported that, in a study of a million women who had received hormone replacement therapies that involved estrogen, those therapies had significantly increased the chances of women over sixty-years-old to develop endometrial cancer of the uterine lining. In the same study, researchers found data linking estrogen and progestogen, a hormone therapy that involves the addition of another hormone, called progesterone, to breast cancer in women over sixty. In addition, a study published in 2002 confirmed that combined estrogen and progestin therapy increased the risk of breast cancer.

In response to those studies, the Endocrine Society published their own statement in 2010 on the involvement of hormone therapies in cancer. They stated that estrogen alone, without a progestogen, increases the risk of endometrial cancer in women on menopausal hormonal therapies. By the early decades of the twenty-first century, physicians prescribed the smallest possible doses to women to mitigate risks of cancer. Many debated the effects of hormone-replacement therapy on women and whether or not the benefits outweigh the risks associated with those therapies.

Sources

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