"Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy" (1948), by Olive Watkins Smith [1]

By: Abboud, Alexis Keywords: Diethylstilbestrol [2] endocrine disruptors [3]

In 1948, Olive Watkins Smith published "Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy" in the *American Journal of Obstetrics and Gynecology.* In 632 women treated with diethylstilbestrol, Smith demonstrated that the drug stimulated the production of progesterone [4], a hormone [5] that regulates the uterine condition during pregnancy [6]. On the basis of her article, and several follow up articles authored by Smith and her husband, George Van Siclen Smith, physicians around the world began prescribing DES to women at risk for pregnancy [6] complications like miscarriage [7] and premature delivery. However, in 1953, researchers found that DES did not prevent pregnancy [6] complications. In 1970, researchers linked fetal exposure to DES to rare and severe cancers later in life. Researchers labeled DES as an endocrine disruptor, a substance that disrupts the hormone [5] system of the body across multiple generations.

Smith worked as a biochemist at the Fearing Research Laboratory in the Free Hospital for Women [8] in Boston, Massachusetts. Her husband worked as a gynecologist and director of the same hospital. Together, Smith and her husband spent much of their careers studying the hormonal cycles of women, particularly during pregnancy [6]. The 1948, "Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy" presents the culmination of Smith's work from the previous ten years. Though only Smith authors the article, she refers to the study as the work of both her and her husband, often using their last name to refer to their work together.

The article starts with an acknowledgement of the 117 obstetricians that followed the requirements of the study laid out by Smith and her husband. Smith next explains the rationale of DES use in pregnancy [6] and the dosage given to the 632 women in the study. Smith then goes through the clinical results of the study. She discusses the results of DES on pregnant women with diabetes or high blood pressure, women who are at risk for spontaneous abortion [9] due to severe bleeding, and women with a previous history of abortions, infertility [10], premature delivery, or surgery on reproductive anatomy.

During the menstrual cycle of women, several hormones [11] act in the body and can be measured in varying levels depending on the time in the cycle. During ovulation [12] when eggs are produced, progesterone [4] levels increase. Once a fertilized egg [13] implants in the uterus [14], the resulting embryo produces human chorionic gonadotropin [15]. Human chorionic gonadotropin [16] maintains the corpus luteum [17], a structure in the ovary [18] that secretes progesterone [4] during pregnancy [6]. Progesterone regulates the conditions in the uterus [14], thickening of the uterine lining called the endometrium [19]. The lining contains blood vessels that deliver nutrients to the developing embryo. If there are deficient amounts of progesterone [4] secreted during the early stages of pregnancy [6], the uterine lining remains thin and unsupportive for development which may lead to miscarriage [7] and other pregnancy [6] complications.

In the beginning of the article, Smith details the findings that led her and her husband to conclude that diethylstilbestrol may be an effective treatment to prevent pregnancy [6] complications like miscarriage [7]. In 1936, Smith and her husband noted that compared to women who were not pregnant, the urine of pregnant women had increased levels of estrogen [20] and decreased levels of chorionic gonadotropin [16] at the tenth week of pregnancy [6]. They hypothesized that increased levels of estrogen [20] in pregnant women enabled the body to the more effectively use chorionic gonadotropin [16]. If the bodies of pregnant women effectively used chorionic gonadotropin [16], then the corpus luteum [17] would be better maintained and more progesterone [4] would be secreted, creating a better environment for the fetus [21] in the womb [22].

In 1939, an experiment by George P. Heckel and Willard M. Allen who worked in Rochester New York, partially confirmed the hypothesis of Smith and her husband by showing that estrogen [20] stimulated progesterone [4] secretion in rabbits. However, Smith and her husband found that natural estrogens in humans [23] does not cause enough of an increase in progesterone [4] secretion for therapeutic applications. A synthetic estrogen [24] like DES, though, could cause a significant increase in progesterone [4] secretion. Smith and her husband showed in 1941 that deficiencies in hormone [5] levels during pregnancy [6] predicted premature deliveries, high blood pressures, fetal deaths, and miscarriages. Thus, they hypothesized that DES may stimulate progesterone [4] secretion and prevent those complications.

After explaining the motivation of the study, Smith presents the dosage regimen used in the study. Smith and her husband recommended that all women in the study take five milligrams of DES per day starting in the sixth week of pregnancy [6], increasing the dosage by five milligrams every two weeks until the fifteenth week, when the women would take twenty-five

milligrams of DES per day. Between the fifteenth and thirty-fifth weeks, the dosage would increase five milligrams every week, until the thirty-fifth week when the women would take 125 milligrams of DES per day. One hundred and twenty-five milligrams is approximately a grape-sized portion of DES. At the end of the thirty-fifth week, women stopped taking DES to mimic the natural drop in hormone [5] levels prior to delivery.

In the next section of the article, Smith details the results of the administration of DES for the prevention of miscarriage [7]. Often, bleeding during pregnancy [6] comes before a miscarriage [7]. Smith used DES to treat two hundred and nineteen women with abnormal bleeding, which may have been precursors to miscarriages, between the sixth and twenty-first weeks of pregnancy [6]. Smith reported that seventy-two percent of those pregnancies resulted in healthy infants. In order to show those births as a significant increase in the number of healthy births in women at risk for miscarriages, Smith refers to a study by pathologists Arthur T. Hertig and Robert G. Livingstone. Hertig and Livingstone who worked in Boston, Massachusetts reported in 1944 that forty percent of all cases of abnormal bleeding without treatment resulted in pregnancies carried to term. Smith reported that if women who had bled abnormally received DES according to her prescribed regimen, then they delivered newborns at a higher rate when compared to no treatment as well as other treatment methods. Thus, Smith concludes not only that DES significantly improves that ability of a pregnant woman to carry a child to term, but also that it is more effective than other treatments.

In the next several sections of the article, Smith discusses the use of DES to prevent pregnancy [6] complications in women with histories of infertility [10], miscarriages, premature deliveries, high blood pressures, diabetes, and complications of late pregnancy [6] like stillbirth. Two hundred and seventy-two women were treated with DES on the basis of a history of infertility [10], abortions, and surgical intervention in the reproductive organs. Of those 272, seventy-eight percent had healthy newborns.

Smith notes that the women she treated had histories of miscarriages. Women with histories of miscarriages have a higher risk of miscarrying again. Hence, if DES prevents a miscarriage [7] in a woman with a history of previous miscarriages, the success lends further credence to the use of DES to prevent miscarriage [7]. Smith cites a 1938 study by physician Percy Malpas who worked in England, where he reported that women who had two consecutive miscarriages had a sixty-two percent chance of carrying their next pregnancy [6] to term, and as the number of previous miscarriages increased, the chance of carrying a child to term decreased. A woman with three previous miscarriages had a twenty-seven percent chance of carrying a fourth pregnancy [6] to term, according to Malpas. However, under Smith's dosage with DES, eighty-seven percent of women with three previous miscarriages carried their fourth pregnancy [6] to term. Smith also notes that if pregnant women receive DES treatment during attempts at conception [25], then that may stimulate progesterone [4] secretion and create a healthier uterine environment.

Halfway through the article, Smith discusses the risks of DES over-dosage, though she discusses those risks as theoretical. Smith states several then-accepted facts about hormones [11]. First, in pregnant rodents given high levels of estrogens, the rodent fetuses die. Second, extended treatment with hormones [11] often permanently damages the secretory activity of organs in the body. However, Smith dismisses those risks for her DES treatments due to the fact that the dosage level with DES never exceeded the natural amount of hormone [5] during pregnancy [6]. Though she does note that in the twenty-eight patients given higher levels of DES than recommended by Smith, fifty-four percent suffered from increased pregnancy [6] complications. Smith concludes that overdoses with DES could result in negative consequences and should be avoided. She also says that 1.4 percent of the 632 women treated with DES suffered side effects like nausea, headaches, and lethargy. However, in five of the nine women who complained of those symptoms, if they continued treatment with DES, the symptoms disappeared. Many women reported that they felt better taking the DES.

Smith concludes that DES is an effective treatment for pregnancy [6] complication and risk of early miscarriage [7]. She states that DES should not be used to treat symptoms later in the pregnancy [6] and that administration with DES must start early in the pregnancy [6].

Later in 1949, Smith and her husband published two further articles regarding the use of DES to treat pregnancy [6] complications. On the basis of those studies, physicians in the US and much of Europe began prescribing DES to millions of women at risk for, or with a history of, pregnancy [6] complications.

In 1953, a group of physicians led by William J. Dieckmann [26] at the University of Chicago [27] in Chicago, Illinois, reported that administration of DES during pregnancy [6] had no effect on the prevention of pregnancy [6] complications. Additionally, in 1970 also at the University of Chicago [27], gynecologist Arthur L. Herbst and pathologist Robert E. Scully reported the increased rate of a rare vaginal cancer, adenocarcinoma of the vagina [28], in young women exposed to DES during their embryonic development. Along with many other studies, that finding spurred the US Food and Drug Administration [29] in Silver Spring, Maryland to ban the use of DES during pregnancy [6] in 1971. After 1971, studies showed that DES causes multiple cancers and reproductive abnormalities in the male and female children of individuals who took DES while pregnant, as well as reproductive abnormalities in the grandchildren of those individuals. Researchers labelled DES as an endocrine disruptor, a substance that disrupts the hormone [5] system of the body causing changes in development. Those changes can affect multiple generations, as in the case of DES.

Sources

1. Dieckmann, William J., M. Edward Davis, L.M. Rynkiewicz, and R.E. Pottinger. “Does the administration of diethylstilbestrol during pregnancy [6] have therapeutic value?” *American Journal of Obstetrics and Gynecology* 66 (1953): 1062–81.
2. Herbst, Arthur L. and Robert E. Scully. “Adenocarcinoma of the vagina [28] in adolescence. A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas).” *Cancer* 25 (1970): 745–7.
3. Hertig, Arthur T., and Robert G. Livingstone. "Spontaneous, threatened and habitual abortion [9]: their pathogenesis and treatment." *New England Journal of Medicine* 230 (1944): 797–806.
4. Heckel, George P., and Willard M. Allen. "Maintenance of the corpus luteum [17] and inhibition of parturition in therabbit [30] by injection of estrogenic hormone [5]." *Endocrinology* 24 (1939): 137–148.
5. Malpas, Percy. "A study of abortion [9] sequences." *BJOG: An International Journal of Obstetrics & Gynecology* 45 (1938): 932–949.
6. Meyers, Robert. *D.E.S.: The Bitter Pill*. Toronto: General Publishing Co., 1983.
7. Smith, George Van Siclen, and Olive Watkins Smith. "The urinary excretion of estrogenic and gonadotropic hormones [11] during menstrual cycles, the period of conception [25] and early pregnancy [6]." *New England Journal of Medicine* 215 (1936): 908–914.
8. Smith, Olive Watkins. “Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy” *American Journal of Obstetrics and Gynecology* 56 (1948): 821–34.

In 1948, Olive Watkins Smith published 'Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy' in the American Journal of Obstetrics and Gynecology. In 632 women treated with diethylstilbestrol, Smith demonstrated that the drug stimulated the production of progesterone, a hormone that regulates the uterine condition during pregnancy. On the basis of her article, and several follow up articles authored by Smith and her husband, George Van Siclen Smith, physicians around the world began prescribing DES to women at risk for pregnancy complications like miscarriage and premature delivery. However, in 1953, researchers at found that DES did not prevent pregnancy complications. In 1970, researchers linked fetal exposure to DES to rare and severe cancers later in life. Researchers labeled DES as an endocrine disruptor, a substance that disrupts the hormone system of the body across multiple generations.

Subject

DES [31] Pregnancy [32] Endocrine disrupting chemicals [33] Hormones [34] Obstetrics [35] Pregnancy--Complications [36] DES (Drug) [37] Endocrine Disruptors [38] Diethylstilbestrol [39] Progesterone [40]

Topic

Publications [41]

Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

Rights

Format

Articles [42]

Last Modified

Wednesday, July 4, 2018 - 04:40

DC Date Accessioned

Tuesday, February 21, 2017 - 21:59

DC Date Available

Tuesday, February 21, 2017 - 21:59

DC Date Created

2017-02-21

DC Date Created Standard

Tuesday, February 21, 2017 - 07:00

- The Embryo Project at Arizona State University, 1711 South Rural Road, Tempe Arizona 85287, United States

---

Links
[1] https://embryo.asu.edu/pages/diethylstilbestrol-prevention-and-treatment-complications-pregnancy-1948-olive-watkins-smith
[2] https://embryo.asu.edu/keywords/diethylstilbestrol
[3] https://embryo.asu.edu/keywords/endocrine-disruptors
[4] https://embryo.asu.edu/search?text=progesterone
[5] https://embryo.asu.edu/search?text=hormone
[6] https://embryo.asu.edu/search?text=pregnancy
[7] https://embryo.asu.edu/search?text=miscarriage
[8] https://embryo.asu.edu/search?text=Free%20Hospital%20for%20Women
[9] https://embryo.asu.edu/search?text=abortion
[10] https://embryo.asu.edu/search?text=infertility
[11] https://embryo.asu.edu/search?text=hormones
[12] https://embryo.asu.edu/search?text=ovulation
[13] https://embryo.asu.edu/search?text=fertilized%20egg
[14] https://embryo.asu.edu/search?text=uterus
[15] https://embryo.asu.edu/search?text=human%20chorionic%20gonadotropin
[16] https://embryo.asu.edu/search?text=gonadotropin
[17] https://embryo.asu.edu/search?text=corpus%20luteum
[18] https://embryo.asu.edu/search?text=ovary
[19] https://embryo.asu.edu/search?text=endometrium
[20] https://embryo.asu.edu/search?text=estrogen
[21] https://embryo.asu.edu/search?text=fetus
[22] https://embryo.asu.edu/search?text=womb
[23] https://embryo.asu.edu/search?text=humans
[24] https://embryo.asu.edu/search?text=synthetic%20estrogen
[25] https://embryo.asu.edu/search?text=conception
[26] https://embryo.asu.edu/search?text=William%20J.%20Dieckmann
[27] https://embryo.asu.edu/search?text=University%20of%20Chicago
[28] https://embryo.asu.edu/search?text=vagina
[29] https://embryo.asu.edu/search?text=Food%20and%20Drug%20Administration
[30] https://embryo.asu.edu/search?text=rabbit
[31] https://embryo.asu.edu/library-congress-subject-headings/des
[32] https://embryo.asu.edu/library-congress-subject-headings/pregnancy
[33] https://embryo.asu.edu/library-congress-subject-headings/endocrine-disrupting-chemicals
[34] https://embryo.asu.edu/library-congress-subject-headings/hormones
[35] https://embryo.asu.edu/library-congress-subject-headings/obstetrics
[36] https://embryo.asu.edu/library-congress-subject-headings/pregnancy-complications
[37] https://embryo.asu.edu/library-congress-subject-headings/des-drug
[38] https://embryo.asu.edu/medical-subject-headings/endocrine-disruptors
[39] https://embryo.asu.edu/medical-subject-headings/diethylstilbestrol
[40] https://embryo.asu.edu/medical-subject-headings/progesterone
[41] https://embryo.asu.edu/topics/publications
[42] https://embryo.asu.edu/formats/articles