

## Does the administration of diethylstilbestrol during pregnancy have therapeutic value? (1950-1952)

### Purpose

- Primary research question(s):
  - Does administration of graduated amounts of DES to pregnant women prevent obstetric complications?
- Primary outcomes:
  - Spontaneous abortion, toxemias of pregnancy, birth weight, prematurity, postmaturity, congenital abnormalities, nausea and vomiting.
- Perceived clinical importance:
  - DES was widely used but not rigorously tested. This is the first controlled clinical trial examining efficacy.

### Background and Context

- In the early 1940's the synthetic estrogen DES (also called stilboestrol) rapidly became popular for a wide variety of treatments including treatment of prostate cancer and post menopausal symptoms, suppression of lactation, post-coital contraception, and prevention of spontaneous abortion.
- In the mid/late 1940's Olive and George Smith of Harvard conducted multiple uncontrolled trials of DES for prevention of miscarriage. Although DES was given primarily to women with high-risk pregnancies, it was also administered to normal pregnant women.
- This is the larger of two randomized placebo-controlled trials conducted in the early 1950's to evaluate efficacy.

### Date and Place Conducted

- Patients enrolled Sept 29, 1950-Nov 20, 1952
- Obstetric practice

### Principal Investigators

- Dieckmann WJ, Davis ME, Rynkiewicz SM, Pottinger RE from the Dept of Obs & Gynec of Univ of Chicago & Chicago Lying-in Hospital

### Sponsored by/source of funding

- Unknown

## Size and Design

- Number of participants: 1646 pregnant women
- Participant characteristics:
  - Characteristics – For primiparas and multiparas average age was 26/29 years, respectively; average height: 162 cm, average weight 57.9-59.8 kilograms; average length of gestation 39 weeks
  - Eligibility criteria – All women registered in prenatal clinic thought to be between 6 and 20 weeks pregnant were eligible. Unlike previous studies, primigravida, primipara and multipara women known to have complications were also included.
- Design:
  - Women registered consecutively at prenatal clinics were assigned a code known only to one individual who was not a clinician. Every other patient was given a placebo. The identity of the two groups was not available until after analysis by the statistician.
  - An initial dose of 5 to 25 mg of either DES or placebo was given to patients depending on period of gestation. Additional doses were graduated according to the regimen proposed by Smith. All tablets included 3 mg of phenol red to trace compliance.
  - Patients were provided an option to opt-out and were (apparently) not informed of either the use of placebos nor use of phenol red to use in urine samples to monitor compliance.
  - Analyses were stratified by parity status.

## Issues Encountered During the Trial

- Because the findings did not concur with trials by Smith et al., both the authors and Eli Lilly analyzed tables to confirm treatment assignments.
- 22% loss to follow-up due to: non-compliance on daily reporting or urine tests (198), women who moved or delivered elsewhere (125), women aborted prior to end of 21 days of meds (52); other reasons such as nausea, not pregnant, etc (141). Uncertain whether these women were equally represented in DES and placebo groups.

## Findings

- Of 840 women on DES and 806 placebo, DES did not reduce the incidence of abortion, prematurity or postmaturity. and may “favor” premature labor. Analysis was of treatment received.

- Premature babies of DES-treated mothers were no longer nor more mature for their gestational ages than comparable prematures in the control group.
- DES did not decrease the incidence of perinatal mortality or frequency of toxemias in pregnancy.

### Impact

- A 1953 double-masked British study of 460 patients by Swyer G and Law RG also found similar results as well as another British placebo controlled double-masked study in 1955 of pregnant diabetic women. These combined findings let the editor of the 1954-55 Year Book of Obstetrics and Gynecology to recommend against prescribing DES to pregnant women.
- It is suggested that the Dieckmann study led to *some* reduction in DES prescriptions. Data suggests that prenatal DES usage in the US peaked in 1950-52, dropped 10% 1953-55, and dropped another 20% 1956-58.
- By 1960, some leading textbooks in obstetrics and gynecology did not recommend the use of DES in pregnancy. (One textbook stopped recommending DES in 1955 citing Dieckmann's study).
- In spite of these few trends, within the context of strong marketing of DES by many companies many clinicians continued to use DES through the 1970's.
- Additional significant research on DES was not published until 1970/1971 when case control studies linked prenatal DES exposure to vaginal clear-cell adenocarcinoma. In 1971 the FDA withdrew approval of DES for use by pregnant women. Until this point, physicians had continued to prescribe DES for use in pregnancy.
- Although this study had little immediate impact on clinical practice, the trial is consistently referred to in chronologies of research on DES.

### Unresolved issues

- Smith et al. resisted these findings arguing that Dieckmann et al. should have included only first-time, normal pregnancies.
- A reanalysis of the data by Brackbill and Berendes was published in 1978 after the long-term carcinogenic and teratogenic effects of DES were known. By using Chi-square tests they found that DES increased the risks for miscarriages, premature births and perinatal death. Several of these findings had been noted in the original study, but went unnoticed in the efforts to challenge the main "null" findings.

## Summary

- This study was the first and remains the largest controlled clinical trial to show that DES was ineffective in the prevention of miscarriage and complications in late pregnancy. In spite of these findings, the drug continued to be prescribed to pregnant women for another 20 years.

## References

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