DES ACTION

Of the Coalition for the Medical Rights of Women

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REVIEW OF THE LITERATURE ON REPRODUCTIVE OUTCOMES IN WOMEN EXPOSED IN UTERO TO DIETHYLSTILBESTROL

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The following pages summarize major published studies of reproductive outcomes among women exposed *in utero* to diethylstilbestrol. DES Action has compiled this summary in order to gain an accessible and comprehensive picture of knowledge currently accumulating about fertility and pregnancy in DES daughters.

We are concerned that attention to single studies or to single effects risks losing sight of what many researchers now consider to be a broader "syndrome" of malformations and malfunctions. Although the incidence of one such malformation, vaginal clear cell adenocarcinoma, is fortunately relatively low, those reflected in "benign" reproductive tract anomalies and impaired reproductive capacity appear far more commonly.

As an organization working to help DES exposed women and men, DES Action offers this summary to health care providers, researchers, and medical students interested in the reproductive status of women exposed prenatally to DES. We all share the goal of increased knowledge about DES effects, and the application of such knowledge to health care which neither overlooks nor overtreats these effects.

A brief description of the varying study samples and designs follows presentation of findings on: structural anomalies; menses; fertility; infertility; ectopic pregnancy; miscarriage; preterm deliveries; total pregnancy outcome. DES Action will add to this summary as new studies are published.

We will also be expanding this summary to include data on DES sons, although woefully few studies exist. DES Action urges that further investigation of DES effects in males be undertaken.

STRUCTURAL ANOMALIES IN DES DAUGHTERS TABLE A

AUTHOR	# OF DES PATIENTS	FOUND ASSOC. BETW. DOSE AMT. & ANOMALIES	FOUND ASSOC. BETW. DOSE ONSET & ANOMALIES	FOUND ASSOC. OF ANOMALIES & ADVERSE PG. OUTCOME	FOUND ASSOC. BETW. UPPER & LOWER TRACT ANOMALIES
BERAL	70	-	X*	-	-
COUSINS	71	-	-	X	-
DECHERNEY	16	-	-	-	X
HERBST ('81)	338	O[1]	O[1]	X[2]	-
KAUFMAN ('77)	60	O	X	-	X
KAUFMAN ('80)	267	O	X*	X*	X*
ROSENFELD	25	-	-	-	X
SANDBERG	167	-	-	X*	-

* For this and all subsequent tables, * denotes statistical significance reported by the author

In this table, "O" is used to indicate that an author looked for a particular association, but did not find it. "-" means the association in question was not examined in the particular study.

[1] Herbst states, "In this study it has not been possible to correlate adverse pregnancy outcome with maternal DES history in regard to the dosage of DES ingested or the time it began in pregnancy because offspring in this study are products of pregnancies in which a standard dosage schedule was used, and there is a narrow distribution of time the mothers entered the study."

[2] Herbst states, "While more of the women who were exposed to DES in the 1st trimester or who had vaginal epithelial changes or cervicovaginal ridges had adverse pregnancy outcomes, the numbers are small and the statistical evidence for association is weak."

MENSES IN DES DAUGHTERS

TABLE B

AUTHOR	# of DES Patients	MENSTRUAL IRREG. DES %	MENSTRUAL IRREG. C %	DYSMENORRHEA DES %	DYSMENORRHEA C %	SHORT FLOW (1-4 days) DES %	SHORT FLOW (1-4 days) C %
BARNES	218	16	10	-	-	-	-
BIBBO	229	18*	10	-	-	60*	43
COUSINS	71	"no difference"		58*	38	47*	20
HANEY	13	47	-	40	-	-	-
HERBST '80	226	10*	4	-	-	-	-
HERBST '81	338	32*	15	-	-	mean flow: 4.3 days*	5 days
PERESS	32	50	-	-	-	-	-
ROSENFELD	25	40	-	-	-	-	-
SCHMIDT	276	28[1]	-	-	-	-	-

[1] An anovulatory type menstrual pattern accounted for 1/3 of these irregularities

* Statistical significance reported by author

FERTILITY IN DES DAUGHTERS TABLE C

AUTHOR	# of DES patients	FERTILITY[1] DES %	C %
BARNES	618	47	50
BIBBO	229	18*	33
COUSINS	71	41	46
HERBST '80			
All study pts.	226	39*	58
Women at risk for pregnancy	132	67*	86
HERBST '81			
Women at risk for pregnancy	338	75*	92
SCHMIDT	276	71	-

[1] Proportion of women pregnant at least once during the period under study. The length of this period varies among the studies. Fertility statistics in these studies do not measure infertility (inability to achieve pregnancy after one or more years of attempts), because they do not report the percentage of women seeking pregnancy but unable to conceive within a year's time.

* Statistical significance reported by author

INFERTILITY IN DES DAUGHTERS TABLE D

AUTHOR	# of DES patients	INFERTILITY[1] DES %	C %
BERGER	69	33.3	-
HERBST '81	338	15.7	6.4
SCHMIDT	106	29.2	-

[1] Inability to achieve pregnancy after 1 or more years of attempts.

ECTOPIC PREGNANCIES IN DES DAUGHTERS TABLE E

AUTHOR	TOTAL # OF PREG.S	EVALUABLE PREGNANCIES[1]	ECTOPICS DES %	ECTOPICS C %
BARNES		220	3.6	1.3
BERGER	80		3.8	-
COUSINS	43		4.7	0
HERBST '80	149		2.7	0
HERBST '81		212	5.7*	.3
KAUFMAN	344		2.6	0
MANGAN	179		4.9*	.03
SANDBERG	225		3.6	-
SCHMIDT	129		5.4	-

[1] Total number of pregnancies minus the number of therapeutic abortions.

* Statistical significance reported by the author.

MISCARRIAGE IN DES DAUGHTERS TABLE F

AUTHOR	# of DES dtrs. with 1 preg.	# of evaluable pregnancies	SPONTANEOUS ABORTIONS DES %	SPONTANEOUS ABORTIONS C %
BARNES	289	220	25.9*	16.1
BERGER	46	62	48.3	-
COUSINS	29	27	18.5	8.8
HERBST '81[1]	150	114	21*	11
KAUFMAN	210	260	32*	8
MANGAN	98	164	18.3*	8.4
SANDBERG	167	164	22	-
SCHMIDT	75	93	25.8	-

[1] First pregnancies only

* Statistical significance reported by author

PRETERM DELIVERIES IN DES DAUGHTERS TABLE G

AUTHOR	# of DES dtrs. with 1 preg.	# of evaluable pregnancies[1]	PRETERM DELIVERIES DES %	PRETERM DELIVERIES C %
BARNES	289	220	7.7	4.5
BERGER	46	62	13	- [2]
COUSINS	29	27	30*	0
HERBST '80	89	116	24*	4.4
HERBST '81[3]	150	114	20*	6
KAUFMAN	210	260	10.7*	3.4
MANGAN	98	164	7.3*	2.2
SANDBERG	167	164	16	-
SCHMIDT	75	93	12.9	-

[1] For this and all other tables in this series, "evaluable pregnancies" refers to all pregnancies with outcomes other than therapeutic abortion. Percentages in the last two columns are based on the number of evaluable pregnancies.

[2] In this and all subsequent tables, a - is used to indicate absence of a control group.

[3] Gives preterm statistics for first pregnancies only.

* Statistical significance reported by author.

TOTAL PREGNANCY OUTCOME IN DES DAUGHTERS TABLE H

AUTHOR	# of DES dtrs. with 1 preg.	# of evaluable pregnancies	VIABLE PREGNANCY OUTCOME DES %	VIABLE PREGNANCY OUTCOME C %
BERGER	46	62	42	-
COUSINS	29	27	58	88
HERBST '80	89	116	65	90
HERBST '81	122[1]	212	67	84
KAUFMAN	210	260	75	92
MANGAN	98	164	75	90
SANDBERG	167	164	69	-
SCHMIDT	75	93	62	-

Note: Authors did not report on statistical significance for these pregnancy outcome statistics.

[1] Number of DES daughters with one or more evaluable pregnancies

NOTES ON SAMPLE SELECTION, STUDY DESIGN, AND JOURNAL OF PUBLICATION OF ARTICLES CITED IN ACCOMPANYING TABLES (first author listed only)

BARNES NEJM 302:609 1980	618 DES daughters from DESAD cohort (this cohort was identified by prenatal record review--see notes on Labarthe study) and 618 controls. Controls were unexposed sisters of study group members, or individuals matched for age and institution where born. Both groups included only women who had had sexual intercourse and no treatment of the vagina or cervix. Control and study groups very similar in regards to age, contraceptive habits and present marital status. Data obtained by record review in combination with annual "DES exam."
BERGER O & G 55:25 1980	Retrospective study of 69 of authors' private patients who had cervical and vaginal abnormalities typical of DES exposure. All were between 18 and 32 years, and "at risk" for pregnancy. Study group followed over 8 year period.
BERAL J Epi & Comm Hlth 35:155, 1981	27 year follow-up study of 136 children whose diabetic mothers were in double-blind randomized trials of DES. Information about children was obtained from hospitals, general practitioners, and other official sources. Those responding to inquiries were unaware of which children were DES vs. placebo-exposed.
BIBBO O & G 49:1 1977	Follow-up study of offspring of mothers who were part of University of Chicago double-blind, placebo-controlled investigation of DES's effectiveness during 1951 and '52. This follow-up study includes 229 DES daughters and 136 controls. Authors did medical record review of both groups, followed by examination by physicians who were unaware of the group (DES or placebo) to which the patient belonged.
COUSINS O & G 56:70 1980	Retrospective investigation of reproductive history of 71 DES-exposed women by comparing their questionnaire data with those of 69 demographically matched non-DES exposed subjects. DES exposed women were all patients at UCSD Oncology Clinic. Controls were patients of UCSD Family Medicine Outpatient Clinic. Response rate was 60.8%. Follow-up on subset of nonrespondents showed no striking differences between respondent and nonrespondent groups.
DECHERNEY FER. & STER. 36:741, 1981	Evaluation of 16 documented DES-exposed women seen at Yale New Haven Hospital Infertility Clinic between Sept. 1977 and Dec. 1980. 12 out of 16 of the women had documented 1st trimester DES exposure.
HANEY FER. & STER. 31:142, 1979	13 DES daughters referred for infertility investigation. Control group consisted of 22 nulliparous women undergoing HSG's as part of infertility investigation.

HERBST
J Repro Med
24:62, 1980

Reproductive histories were compared for 226 DES exposed and 203 nonexposed daughters whose mothers were part of double-blind, placebo-controlled trials of DES at University of Chicago. All subjects were interviewed at time of follow-up gyn visits, or by telephone or mail if unable to come for examination. All participants knew whether their mothers had taken DES or a placebo. No known selection bias for the completed questionnaires, which were obtained for 60% of the exposed and 53% of the unexposed.

HERBST
AJOG 141:1019
1981

Information on reproductive history, gyn operations and examinations was analyzed for 338 DES exposed and 298 unexposed women whose mothers were in University of Chicago trials (see above). Interviews were completed during the clinic visit, by telephone interview or by mail. Medical record reviewer did not know DES exposure status of subjects.

KAUFMAN
AJOG 128:51
1977

Report on 60 DES exposed women from DESAD study who volunteered for HSG's. Maternal and patient histories, complete gyn exam, and HSG obtained for all 60 women. Control group consisted of 23 women who had HSG performed as part of an infertility investigation. 7 of the 23 controls were confirmed as non-DES exposed. Similar mean age and history of prior pregnancies in both groups.

KAUFMAN
AJOG 137:299
1980

267 DES daughters from DESAD who volunteered for HSG's after indications for this test were explained. No special effort was made to recruit individuals with previously documented abnormal physical findings. Comparison groups of 34 women having HSG's as part of infertility investigation. Additional group of 117 parous DES daughters who hadn't undergone HSG's and comparison group of 87 parous controls from DESAD study.

LABARTHE
O & G 51:453
1978

DESAD study group, 40% of which consisted of participants identified by review of prenatal records of consenting physicians and clinics from geographic areas served by major medical centers. The rest of the study group was made up of women documented as DES exposed but walking in (25%), women referred to the DESAD project (23%), and women not documented as exposed but having gyn abnormalities typical of DES exposure (12%). Comparison group consisted of unexposed sisters or matched controls (matched for age of participant and age of mother). Data gathered from medical records, health history and exam. Total of 2,940 women in DES group.

MANGAN
O & G 59:315
1982

Review of obstetric medical histories of 98 DES daughters who were patients of U. of Penn. Gyn-Onc Screening Clinic. Three separate control groups consisting of 167 age-matched normal women, 20 unexposed parous women, and mothers of the 98 DES daughters. All patients in DES exposed population had some objective evidence of exposure--either adenosis or a DES-associated structural abnormality.

ROSENFELD O & G 55:453 1980	Record review of 25 DES-exposed women under treatment by the authors for reproductive dysfunction. Purpose of study was to review clinical findings with hope of finding possible mechanisms of infertility in DES daughters.
SANDBERG AJOG 140:194 1981	Retrospective interviews with 167 parous DES daughters seen through Stanford Stilbestrol Clinic. These women were either self-referred or physician-referred, and none was intentionally located through prenatal record review. Sandberg also summarizes and compares findings of other recent studies assessing pregnancy outcomes of DES daughters.
SCHMIDT FER. & STER. 33:21 1980	Evaluation of 276 DES exposed women who were self-referred to University of No. Carolina "DES Clinic" and who responded to mailed questionnaire. The questionnaire was mailed to 287 women, of whom 11 failed to respond. Histories were obtained from all respondents followed by exam (including colposcopy).

NOTE: A review article by Robert Stillman covers additional categories of reproductive tract pathology, as well as reproductive outcome, in women and men exposed in utero to DES (Stillman, R.J., "In utero Exposure to Diethylstilbestrol: Adverse Effects on the Reproductive Tract and Reproductive Performance in Male and Female Offspring," American Journal of Obstetrics and Gynecology, Vol. 142, No. 7, April, 1982).

Note on implications of study design: Many of the studies listed above are based on a record review approach. Record review is valuable for estimating overall incidence of a problem in the exposed population. However, a separate question is whether identifiable sub-populations exist; e.g. DES daughters with structural anomalies, doctor-referred DES daughters, self-referred DES daughters etc., for whom total population figures are not the best predictor.

Addendum:

HANEY J of Repro Med. 28:851 1983	Evaluation of 33 self- and physician-referred infertile couples in whom the woman had been exposed to DES in utero. The authors sought to determine whether a unique pattern of reproductive problems exists in the DES exposed population.

Formulario sugerido para el histori al clinico de pacientes expuestos al DES

Nombre_____ Fecha de nacimiento _____

Dirección_____

Mujeres y hombres nacidos después de 1940:

?Tuvó su madre alguna dificultad mientras lo llevó a ud dentro de su vientre?

Si_____ No_____ No sabe_____

?Tuvó su madre dificultades durante cualquiera de sus embarazos? (manchas de sangre, abortos)

Si_____ No_____ No sabe_____

?Tomó su madre algun tipo de medicamentos (hormonas) durante su embarazo con ud?

Si_____ ?Que tipo? No_____

Si ud no sabe, ?puede averiguar con su madre, con el médico que la atendió o con el hospital donde ud nació, si su madre tomó algun tipo de medicamentos minetras estuvo embarazada con ud?

Si_____ No_____

(Para mujeres) ?Ha tenido problemas con sus mestruaciones, descargos vaginales u otros sintomas? En caso positivo, describa.

* * * * * * * *

Para mujeres que quedaran embarazadas después de 1940:

?Tuvó ud alguna dificultad (manchas de sangre, abortos) durante sus embarazas?

Si_____ No_____

?Tomó ud algun medicamento (hormonas) durante sus embarazos?

Si_____ No_____

En caso positivo, ?que tipo?

Si ud no recuerda que tipó de medicamentos tomo durante sus embarazas, ?puede averiguar con su doctor o con el hospital donde ud dió a luz e informarnos?

Si_____ No_____

DES Action is compiling a directory of providers familiar with conditions related to DES exposure. If you wish to be included in this directory, please complete this page and return it to DES Action,

1. Name_____

2. Address_____Phone_____

   Board Certified?_____Hospital Affiliations_____

3. In a routine exam, do you ask about DES exposure?____Do you check for exposure if DES history is unknown?____suspected?____If so, how?_____

4. How many DES exposed patients do you see per year?____Are you taking new patients?_____

5. If you do not monitor DES exposed patients, to whom do you refer?_____

6. If you do follow DES daughters, under what conditions do you employ:

   Iodine stain (Schiller or Lugol's test)_____

   Colposcopy_____

   360° Vaginal Pap Smear_____

   Palpation_____

   Biopsy_____

7. In your opinion, how frequently should DES daughters receive follow-up exams?_____

8. How do you explain the patient's condition to her? (after exam, during exam, with pamphlets, diagrams?)_____

9. What methods of contraception do you recommend for DES daughters? Pill____ IUD____Diaphragm____Other_____

10. Approximate cost of initial screening?____Subsequent exams?____Are sliding scale payment procedures available?____Medi-Cal?____

11. Have you encountered infertility or subfertility problems in DES daughters? _____If so, do you manage these cases or refer them out?_____

12. Do you follow pregnant DES daughters?_____If yes, please indicate whether you monitor DES daughters more closely for their higher risk of:

    Ectopic pregnancy___If yes, how?_____

    Spontaneous abortion____If yes, how?_____

    _____

    Preterm labor (premature cervical dilatation and/or excessive uterine activity)____If, yes, how?_____

    _____

13. Would you be interested in DES patient literature for your office?_____

14. Comments_____

    _____