Psychological Medicine, 2007, **37**, 1315–1322. © 2007 Cambridge University Press
doi:10.1017/S0033291707000438 First published online 4 April 2007 Printed in the United Kingdom

Serious psychiatric outcome of subjects prenatally exposed to diethylstilboestrol in the E3N cohort study

HELENE VERDOUX[1], JACQUES ROPERS[2], DOMINIQUE COSTAGLIOLA[3], FRANÇOISE CLAVEL-CHAPELON[4] AND XAVIER PAOLETTI[5]*

[1] *INSERM U657*; *Université Segalen-Bordeaux 2*, *Bordeaux*, *France*; [2] *Agence Française de Sécurité Sanitaire des Produits de Santé*, *St Denis*, *France*; [3] *INSERM U720*, *Paris*, *France*; [4] *INSERM*, *Equipe E3N*, *Villejuif*, *France*; [5] *INSERM U738*, *Paris*, *France*

ABSTRACT

Background. Prenatal exposure to diethylstilboestrol (DES) may induce neurodevelopmental disturbances potentially mediating an increased risk of psychiatric disorders in exposed subjects. Most findings of an increased prevalence of psychiatric disorders in men and women prenatally exposed to DES are not easy to interpret because of selection biases.

Method. Information on hormonal treatment during pregnancy and on offspring's medical outcome was collected from women participating in the Etude Epidemiologique de femmes de la Mutuelle Générale de l'Education Nationale (E3N) prospective cohort who completed consecutive postal questionnaires on a range of medical events since 1990. Information on hormonal treatment during pregnancy was collected in 1992 and on offspring's medical outcome in 2004. The psychiatric outcome of subjects prenatally exposed to DES was compared to that of their unexposed siblings.

Results. A total of 1352 mothers with DES treatment for at least one pregnancy provided information on 1680 exposed children and 1447 unexposed siblings. After adjustment for duration of follow-up, educational level, history of obstetric complication, prenatal exposure to progestagen drugs or other hormones and parental history of psychiatric hospitalization, no association was found between prenatal exposure to DES and occurrence of strictly defined serious psychiatric outcome (suicide or psychiatric hospitalization) [adjusted odds ratio (OR) 0·8, 95% confidence interval (CI) 0·5–1·2], or of broadly defined serious psychiatric outcome (same events plus psychiatric or psychological consultation) (adjusted OR 1·0, 95% CI 0·8–1·2).

Conclusions. These findings suggest that the impact of prenatal DES exposure on foetal brain development, if any, is unlikely to increase the risk of serious psychiatric disorders.

INTRODUCTION

There is accumulating evidence that subjects with perinatal exposure to environmental events disturbing neurodevelopment are at increased risk of psychiatric disorders (Murray & Lewis, 1987; Cannon *et al*. 2003; Verdoux, 2004). Few studies have investigated the impact of prenatal exposure to synthetic hormones on psychiatric outcome. However, intra-uterine levels of oestrogens affect foetal brain development, particularly cerebral lateralization (Geschwind & Galaburda, 1985). Synthetic oestrogens (or xeno-oestrogens) have a non-steroidal structure and do not bind to peripheral alpha-foetoprotein, a mechanism preventing entry into the foetal central nervous system; unlike endogenous oestrogens, they do not convert to oestrone, a metabolite of low oestrogenic activity (Schachter, 1994). Hence, high concentrations of active xeno-oestrogens reach the foetal brain with potential deleterious consequences on brain development (Slikker *et al*. 1982).

* Address for correspondence: Xavier Paoletti, Institut National du Cancer, Department of Clinical Research and Biostatistics, 52 avenue Morizet, 92513 Boulogne cedex, France.
(Email: xpaoletti@institutcancer.fr)

Animal studies have shown that rodents prenatally exposed to xeno-oestrogens such as diethylstilboestrol (DES) or ethynyloestradiol present with a range of behavioural abnormalities (Porrini *et al*. 2005). Human studies suggest that DES may impact on the neurodevelopmental lateralization process. An excess of left-handedness in women with prenatal exposure to DES has been reported by several studies (Schachter, 1994; Scheirs & Vingerhoets, 1995; Smith & Hines, 2000), although this finding was not supported by others (Titus-Ernstoff *et al*. 2003); yet other studies found an excess of left-handedness in men with prenatal exposure to DES (Reinisch & Sanders, 1992; Titus-Ernstoff *et al*. 2003).

Considering that abnormal lateralization may be implicated in the pathophysiology of psychiatric disorders (Crow *et al*. 1996; Orr *et al*. 1999), DES-induced neurodevelopmental disturbances may potentially mediate an increased risk of psychiatric disorders in exposed subjects. Contradictory findings have been reported by previous studies exploring this issue (Vessey *et al*. 1983; Meyer-Bahlburg *et al*. 1985; Ehrhardt *et al*. 1987; Fried-Cassorla *et al*. 1987; Gustavson *et al*. 1991; Pillard *et al*. 1993; Titus-Ernstoff *et al*. 2003).

Although DES is no longer prescribed, its impact on psychiatric outcome should be clarified, considering the numerous subjects prenatally exposed to DES up to the 1970s (around 8000 in UK, more than 150 000 in the Netherlands and in France and nearly 5 million in the USA; Palmlund *et al*. 1993). Furthermore, because of the persisting risk of prenatal exposure to environmental xeno-oestrogens (Newbold, 2004), DES studies are of value as a model of exposure to these substances. We investigated, in the French prospective cohort Etude Epidemiologique de femmes de la Mutuelle Générale de l'Education Nationale (E3N), whether psychiatric outcome differed between subjects prenatally exposed to DES and their unexposed siblings.

METHOD

Sample

Participants were mothers of a subgroup of the E3N cohort who completed questionnaires about their children for the present study. The E3N was initiated in 1990 to study risk factors for cancer in women (Clavel-Chapelon, 2002; Romieu *et al*. 2003; Fournier *et al*. 2005; Tehard *et al*. 2005). At baseline, the cohort included 97 995 women fulfilling the following inclusion criteria: (i) born between 1925 and 1950; (ii) covered by the national health insurance plan for French teachers (MGEN); and (iii) giving written informed consent to participate in the investigation. Information on a range of medical events is collected using postal questionnaires approximately every 24 months since 1990.

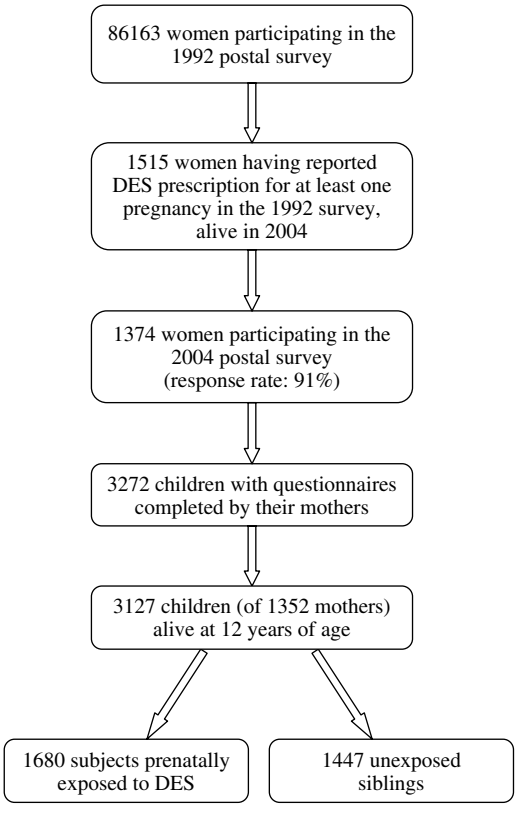

FIG. 1. Selection of the subjects prenatally exposed to DES and their unexposed siblings.

The process for subject selection included in the present study is presented in Fig. 1. Information on hormonal treatments during pregnancy was collected in the 1992 questionnaire sent to the whole cohort and completed by 87·9% of the women included at baseline. From this initial pool, we identified all women still alive who reported giving birth to at least one child exposed to DES *in utero*. They were sent a

https://doi.org/10.1017/S0033291707000438 Published online by Cambridge University Press

Table 1. *Characteristics of subjects prenatally exposed to DES and their unexposed siblings*

	Subjects with prenatal DES exposure *n* (%) or mean (S.D.) (*n* = 1680)	Siblings without prenatal DES exposure *n* (%) or mean (S.D.) (*n* = 1447)
Demographic characteristics		
Duration of follow-up (years)[a]	36·8 (7·4)	36·5 (5·5)
Male gender	751 (44·7)	781 (54·0)
Educational level >14 years	1189 (71·8)	952 (67·2)
Obstetric history		
Definite obstetric complication[b]	1331 (79·2)	561 (38·8)
Prenatal exposure to progestagen	632 (37·6)	281 (19·4)
Prenatal exposure to other hormones	87 (5·2)	75 (5·2)
History of maternal or paternal psychiatric hospitalization	74 (4·4)	61 (4·2)

DES, Diethylstilboestrol; S.D., standard deviation.

[a] Age of the children still alive in 2004, or age at the time of death.

[b] At least one definite obstetric complication according to the Lewis and Murray scale (Lewis & Murray, 1987): threatened abortion; antepartum bleeding; severe hypertension requiring hospitalization; caesarean for emergency delivery; breech presentation; premature birth >3 weeks; postmature birth >2 weeks; birthweight <2000 g; incubator used >4 weeks.

postal questionnaire in 2004. The cover letter mentioned only that the aim of the survey was to explore the impact of perinatal events on children's health. The hypothesis addressed in the present study and the fact that women had been selected on the basis of their prior answer to the DES item were not specified.

Assessment of prenatal exposure to DES and other hormones

According to the information reported by the mother in the 1992 questionnaire, three variables were derived for each child: prenatal exposure to (i) DES; (ii) progestagen drugs; (iii) other hormones. To facilitate accurate recall, a leaflet with colour photographs of the hormonal treatments marketed in France accompanied the questionnaire. The presence or absence of hormonal treatment was recorded, without further information on motive for prescription, dose, duration or stage of pregnancy.

Assessment of child's outcome

In 2004, the women were asked to complete a questionnaire for each biological child born alive (up to five). Information collected included (i) history of obstetric complications using questions (see Table 1) derived from the Lewis and Murray scale (this scale has been widely used to explore the association between obstetric complications and psychiatric outcome in studies based upon maternal recall; Lewis & Murray, 1987; Verdoux *et al.* 1997); (ii) demographic characteristics, including cause of death; (iii) reproductive status: parity, history of miscarriage and of difficulties to conceive; if the answer was positive to the latter item, the mother was asked to specify if, to her knowledge, these difficulties were attributable to her child, to her partner, or of unknown origin; nulliparity and difficulties to conceive attributable to her child were categorized as 'infertility strictly defined', nulliparity and difficulties to conceive not attributable to the child or of unknown origin were categorized as 'infertility broadly defined'; (iv) lifetime medical history of hospitalization or consultation with specialists, and age at first hospitalization: women were proposed a list of 15 possible reasons for hospitalization (including psychiatric hospitalization) and a similar list of speciality names (including consultation with a psychiatrist or a psychologist). We defined two categories of psychiatric outcome: (i) lifetime history of strictly defined serious psychiatric outcome if the mother reported that her son or daughter committed suicide or had been hospitalized in psychiatry; and (ii) lifetime history of broadly defined serious psychiatric outcome including the previous events or a history of consultation with a psychiatrist or a psychologist.

In addition, history of hospitalization in the first- and second-degree biological relatives of each child was collected. The above list of medical motives was used. In the present study only information on psychiatric hospitalization was used as a proxy measure of family history of

https://doi.org/10.1017/S0033291707000438 Published online by Cambridge University Press

psychiatric disorder. We applied a narrow definition of positive family history of psychiatric disorder, restricted to history of psychiatric hospitalization in the mother or in the biological father.

Statistical methods

We investigated the relationship between exposure to DES and psychiatric outcome overall and after stratification by gender. We also explored the relationship between DES exposure and reproductive status in daughters (history of miscarriage, nulliparity and infertility) to serve as a tool to validate maternal information, as the increased frequency of such events in DES-daughter has been largely documented elsewhere (Kaufman *et al.* 2000). Finally, we performed a sensitivity analysis to check that removing non-significant variables or modifying correlation structure did not modify the other estimates (results available on request).

Characteristics of the exposed and unexposed children were compared statistically using the χ^2 test. Multivariate analyses were performed to assess associations between each outcome of interest and exposure to DES, progestagen drugs or other hormones. The models were adjusted for follow-up duration (calculated as the age for children still alive in 2004 or the age at death), sex, educational level (dichotomized as above or below 14 years), history of obstetric complications and family history of psychiatric hospitalization. All variables except follow-up were treated as binary. Because of the large sample size, model selection was unnecessary, thereby limiting the risk of bias. Separate models were generated for strictly and broadly defined serious psychiatric outcomes. All variables included in the models were specified in the analysis plan blind to the data.

To take into account intra-family correlation, a hierarchical two-level logistic model was used (Watier *et al.* 1997). The child's level was embedded in the family level, making it possible to estimate and to take into account correlation between siblings. An exchangeable correlation structure assuming common correlation among all siblings was used. The generalized estimating equations (GEE) approach provided estimates and 95% confidence intervals (CIs). Adjusted odds ratios (aORs) are reported. All tests were two-tailed. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of the sample

Numbers of respondents and children included in the study are given in Fig. 1. Few data were missing for most items of the questionnaire, limiting *a posteriori* loss of power; obstetrical complications variables had the highest frequency of missing data (around 10%) but sensitivity analyses with different imputation strategies led to the same results. The mean age of the mothers was 65 years (S.D. = 5·8, range 54–80). Only children alive at 12 years of age and without history of psychiatric hospitalization before age 12 were considered, in order to exclude subjects with severe infancy or childhood psychiatric disorders such as mental retardation or pervasive development disorders, because inclusion of these subjects may have contributed to increase the heterogeneity of the spectrum of disorders considered in the psychiatric outcome. The mean duration of follow-up was 36 years (S.D. = 6·4, range 12–57) and was 30 years and over for most (90%) children.

The characteristics of the subjects with prenatal DES exposure and of their unexposed siblings are given in Table 1. Irrespective of exposure status, most subjects had a high educational level. Nearly four out of five children prenatally exposed to DES had a history of definite obstetric complications, the most frequent being threatened abortion (69·7% of DES-exposed subjects; 21·4% of unexposed siblings) and antepartum bleeding (41·8% of DES-exposed subjects; 13·5% of unexposed siblings). Statistical tests indicate that both groups are not significantly different for all characteristics except for sex, progestagen exposure and obstetrical complications. These two latter differences were expected because DES was given to pregnant women with a history of prior complicated pregnancy and was often co-prescribed with progestagens.

Prenatal hormonal exposure and psychiatric outcome

In the overall sample, subjects ($n = 16$) who committed suicide had a median age of 27 years

https://doi.org/10.1017/S0033291707000438 Published online by Cambridge University Press

Table 2. *Psychiatric outcome of subjects prenatally exposed to DES and their unexposed siblings*

	Subjects with prenatal DES exposure *n* (%)	Siblings without prenatal DES exposure *n* (%)	Adjusted OR (95% CI)[a]
Suicide	9 (0·5)	7 (0·5)	
Psychiatric hospitalization	60 (3·6)	55 (3·8)	
Strictly defined serious psychiatric outcome[b]	60 (3·6)	58 (4)	0·8 (0·5–1·2), $p=0·22$
Consultation with a psychiatrist	194 (11·6)	147 (10·2)	
Consultation with a psychologist	199 (11·9)	162 (11·2)	
Broadly defined serious psychiatric outcome[c]	330 (19·6)	267 (18·5)	1·0 (0·8–1·2), $p=0·86$

DES, Diethylstilboestrol; OR, odds ratio; CI, confidence interval.

[a] Adjusted for duration of follow-up, educational level, history of at least one definite obstetric complication according to the Lewis and Murray scale (Lewis & Murray, 1987) (see Table 1), prenatal exposure to progestagen drugs or other hormones, paternal or maternal history of psychiatric hospitalization.

[b] Suicide or psychiatric hospitalization.

[c] Suicide, psychiatric hospitalization or consultation with a psychiatrist or a psychologist.

[interquartile range (IQR) 23–31, range 18–43]. The median age at first psychiatric hospitalization was 24 years (IQR 20–32, range 13–47). The comparison of psychiatric outcome according to prenatal DES exposure status is given in Table 2.

Subjects prenatally exposed to DES were not at increased risk of presenting with a lifetime history of suicide or psychiatric hospitalization compared to their unexposed siblings. No association was found between prenatal DES exposure and serious psychiatric outcome broadly defined. Similar findings were obtained in analyses stratified by gender: the occurrence of strictly defined serious psychiatric outcome did not differ between women prenatally exposed to DES and their unexposed sisters (aOR 0·8, 95% CI 0·5–1·4, $p=0·49$) or between men exposed to DES and their unexposed brothers (aOR 0·80, 95% CI 0·37–1·67, $p=0·56$).

In the model adjusted for DES exposure and other potential confounding factors (see Table 1), no association was found between (i) prenatal exposure to progestagen drugs and serious psychiatric outcome (strictly defined: aOR 1·2, 95% CI 0·8–1·9, $p=0·33$; broadly defined: aOR 1, 95% CI 0·8–1·2, $p=0·99$); (ii) prenatal exposure to other hormones and serious psychiatric outcome (strictly defined: aOR 0·8, 95% CI 0·3–1·8, $p=0·57$; broadly defined: aOR 1·2, 95% CI 0·8–1·7, $p=0·41$).

Prenatal exposure to hormones and daughters' obstetrical outcome during adulthood

The frequency of nulliparity did not differ between daughters prenatally exposed to DES compared to their unexposed sisters [$n=229$ (27·1%) *v.* $n=156$ (26·6%), aOR 1·1, 95% CI 0·8–1·4, $p=0·52$]. A history of miscarriage was more frequently reported in daughters prenatally exposed to DES compared to their unexposed sisters [$n=189$ (22·3%) *v.* $n=97$ (16·5%), aOR 1·4, 95% CI 1·1–1·9, $p=0·01$]. Significant associations were found between prenatal DES exposure and infertility strictly defined [exposed daughters $n=79$ (9·4%) *v.* unexposed sisters $n=16$ (1·7%), aOR 3·4, 95% CI 2·0–6·0, $p=0·0001$] or infertility broadly defined [exposed daughters $n=110$ (13·1%) *v.* unexposed sisters $n=42$ (7·2%), aOR 2·1, 95% CI 1·4–3·1, $p=0·0001$]. No association was found between prenatal exposure to progestagen drugs and nulliparity (aOR 1·1, 95% CI 0·8–1·4, $p=0·55$), history of miscarriage (aOR 0·9, 95% CI 0·7–1·2, $p=0·52$), and infertility strictly (aOR 1·4, 95% CI 0·9–2·2, $p=0·18$) or broadly (aOR 1·2, 95% CI 0·8–1·7, $p=0·36$) defined. No association was found between prenatal exposure to other hormones and nulliparity (aOR 1·0, 95% CI 0·6–1·6, $p=0·90$), history of miscarriage (aOR 1·1, 95% CI 0·6–2·1, $p=0·77$), and infertility strictly (aOR 0·6, 95% CI 0·2–1·8, $p=0·31$) or broadly (aOR 1·1, 95% CI 0·5–2·3, $p=0·84$) defined.

DISCUSSION

Serious psychiatric outcome did not differ between subjects prenatally exposed to DES and their unexposed siblings. A history of miscarriage and of infertility was more frequent in women prenatally exposed to DES compared to their unexposed sisters.

https://doi.org/10.1017/S0033291707000438 Published online by Cambridge University Press

Strengths and weaknesses

First, memory bias may limit the validity of maternal recall on pregnancy events, particularly medications prescribed during pregnancy. As we have little reason to suspect that this bias differed systematically according to offspring's psychiatric outcome, such a misclassification may have contributed to reduce the strength of the association. However, information on DES exposure was collected 14 years before the present survey, the mothers were not informed about the aim of this study, and their report of DES impact on their daughters' obstetric outcome at adulthood was in accordance with the documented genital consequences of DES (Kaufman *et al.* 2000). Second, mothers may not be fully informed about the psychiatric outcome of their children, such as psychiatric consultation, but it is unlikely that they were not aware of events such as suicide or psychiatric hospitalization, or that they systematically under-reported psychiatric events for DES-exposed subjects compared to their unexposed siblings. However, we cannot exclude a non-systematic misclassification of broadly defined serious psychiatric outcome that may have attenuated the strengths of the associations. Third, mothers and children were not representative of the general population with regard to educational level, but is it unlikely that educational level modifies the neurodevelopmental impact of prenatal DES exposure. Fourth, no information was available on duration, dose and time of DES exposure during pregnancy, which may have attenuated the strength of the association if these characteristics modify the impact of DES exposure on psychiatric outcome. However, such information was no more available in prior studies reporting an association between DES exposure and increased risk of psychiatric disorders.

The major strengths of the study are the high response rate, the large sample size limiting the risk of type II error, and the fact that most offspring had passed beyond the age of peak incidence of major psychiatric disorders. In particular, for a prevalence of psychiatric disorders around 10% and an intra-family correlation between 0% and 50%, the study had a 80% power to detect a non-adjusted OR between 1·3 and 1·1 respectively.

Interpretation of findings

Studies have reported that the prevalence of psychiatric disorders, particularly depression or eating disorders, is increased in women or men prenatally exposed to DES (Vessey *et al.* 1983; Meyer-Bahlburg *et al.* 1985; Gustavson *et al.* 1991; Pillard *et al.* 1993). Most of these studies were hampered by selection biases, the sampling procedure selecting, for example, women recruited in DES specialized centres or members of users' associations (Verdoux, 2002). The only exception was the study by Vessey (1983) using data from a randomized controlled trial performed in the 1950s comparing DES to placebo in 1000 women. Information on the medical outcome of their 660 children was provided in 1977–1982 by their general practitioners (GPs) blind to the exposure status. Subjects prenatally exposed to DES were twice as likely to present with psychiatric disorders, mostly anxiety and depression, compared to their unexposed siblings. Other studies did not report such an association (Ehrhardt *et al.* 1987; Fried-Cassorla *et al.* 1987; Titus-Ernstoff *et al.* 2003). The discrepancy between our findings and those of previous studies showing an excess of psychiatric disorders in subjects prenatally exposed to DES may be explained by the selection biases present in most prior studies. As psychiatric outcome was restricted in the present study to suicide or treatment by mental health professionals, we did not consider most common mental disorders treated at a primary care level, which may explain the difference between our findings and those reported in the study by Vessey *et al.* (1983).

Compared to prior studies carried out in selected populations or those that did not differentiate psychiatric outcome according to severity level or need for care, the major contribution of the present study is to provide strong evidence that prenatal exposure to DES is not associated with an increased risk of major psychiatric disorder requiring hospitalization or at least consultation with a mental health specialist. Our findings suggest that prenatal DES exposure is unlikely to have a major impact on the development of foetal brain structures implicated in the pathophysiology of serious psychiatric disorders. Nevertheless, this reassuring finding should not obscure the fact

that DES-exposed subjects, particularly DES daughters, too often have to cope daily with the psychological distress induced by cancer or the consequences of genital malformations (infertility, foetal loss), and have to be provided with adequate psychological support.

ACKNOWLEDGEMENTS

We are grateful to the users' association Union Nationale des Amis et Familles de Malades Psychiques (UNAFAM) for supporting the study logistically. We thank the French League against Cancer, the European Community, the 3M Company, the Mutuelle Générale de l'Education Nationale, and the French Drugs Regulatory Agency (Agence Française de Sécurité Sanitaire des Produits de Santé) for supporting the E3N study financially. We thank LyAn Hoang for collecting the data and for managing the database and Ray Cooke for supervising the English of this manuscript. We acknowledge the reviewers of a prior version of the manuscript for their thoughtful comments.

DECLARATION OF INTEREST

None.

REFERENCES

Cannon, M., Kendell, R., Susser, E. & Jones, P. (2003). Prenatal and perinatal risk factors for schizophrenia. In *The Epidemiology of Schizophrenia* (ed. R. Murray, P. Jones, E. Susser, J. Van Os and M. Cannon), pp. 74–99. Cambridge University Press: Cambridge.

Clavel-Chapelon, F. (2002). Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. *British Journal of Cancer* **86**, 723–727.

Crow, T. J., Done, D. J. & Sacker, A. (1996). Cerebral lateralization is delayed in children who later develop schizophrenia. *Schizophrenia Research* **22**, 181–185.

Ehrhardt, A. A., Feldman, J. F., Rosen, L. R., Meyer-Bahlburg, H. F., Gruen, R., Veridiano, N. P., Endicott, J. & Cohen, P. (1987). Psychopathology in prenatally DES-exposed females: current and lifetime adjustment. *Psychosomatic Medicine* **49**, 183–196.

Fournier, A., Berrino, F., Riboli, E., Avenel, V. & Clavel-Chapelon, F. (2005). Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *International Journal of Cancer* **114**, 448–454.

Fried-Cassorla, M., Scholl, T., Borow, L., Strassman, H. & Bowers, E. (1987). Depression and diethylstilbestrol exposure in women. *Journal of Reproductive Medicine* **32**, 847–850.

Geschwind, N. & Galaburda, A. (1985). Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and program for research. *Archives of Neurology* **42**, 521–552.

Gustavson, C. R., Gustavson, J. C., Noller, K. L., O'Brien, P. C., Melton, L. J., Pumariega, A. J., Kaufman, R. H. & Colton, T. (1991). Increased risk of profound weight loss among women exposed to diethylstilbestrol in utero. *Behavioral and Neural Biology* **55**, 307–312.

Kaufman, R. H., Adam, E., Hatch, E. E., Noller, K., Herbst, A. L., Palmer, J. R. & Hoover, R. N. (2000). Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. *Obstetrics and Gynecology* **96**, 483–489.

Lewis, S. & Murray, R. (1987). Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *Journal of Psychiatry Research* **21**, 413–421.

Meyer-Bahlburg, H. F., Ehrhardt, A. A., Feldman, J. F., Rosen, L. R., Veridiano, N. P. & Zimmerman, I. (1985). Sexual activity level and sexual functioning in women prenatally exposed to diethylstilbestrol. *Psychosomatic Medicine* **47**, 497–511.

Murray, R. & Lewis, S. W. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal* **295**, 681–682.

Newbold, R. R. (2004). Lessons learned from perinatal exposure to diethylstilbestrol. *Toxicology and Applied Pharmacology* **199**, 142–150.

Orr, K. G., Cannon, M., Gilvarry, C. M., Jones, P. B. & Murray, R. M. (1999). Schizophrenic patients and their first-degree relatives show an excess of mixed-handedness. *Schizophrenia Research* **39**, 167–176.

Palmlund, I., Apfel, R., Buitendijk, S., Cabau, A. & Forsberg, J. G. (1993). Effects of diethylstilbestrol (DES) medication during pregnancy: report from a symposium at the 10th International Congress of ISPOG. *Journal of Psychosomatic Obstetrics and Gynecology* **14**, 71–89.

Pillard, R. C., Rosen, L. R., Meyer-Bahlburg, H., Weinrich, J. D., Feldman, J. F., Gruen, R. & Ehrhardt, A. A. (1993). Psychopathology and social functioning in men prenatally exposed to diethylstilbestrol (DES). *Psychosomatic Medicine* **55**, 485–491.

Porrini, S., Belloni, V., Della Seta, D., Farabollini, F., Giannelli, G. & Dessi-Fulgheri, F. (2005). Early exposure to a low dose of bisphenol A affects socio-sexual behavior of juvenile female rats. *Brain Research Bulletin* **65**, 261–266.

Reinisch, J. M. & Sanders, S. A. (1992). Effects of prenatal exposure to diethylstilbestrol (DES) on hemispheric laterality and spatial ability in human males. *Hormones and Behavior* **26**, 62–75.

Romieu, I., Avenel, V., Leynaert, B., Kauffmann, F. & Clavel-Chapelon, F. (2003). Body mass index, change in body silhouette, and risk of asthma in the E3N cohort study. *American Journal of Epidemiology* **158**, 165–174.

Schachter, S. (1994). Handedness in women with intrauterine exposure to diethystilbestrol. *Neuropsychologia* **32**, 619–623.

Scheirs, J. G. & Vingerhoets, A. J. (1995). Handedness and other laterality indices in women prenatally exposed to DES. *Journal of Clinical and Experimental Neurophysiology* **17**, 725–730.

Slikker Jr., W., Bailey, J. R., Newport, D., Lipe, G. W. & Hill, D. E. (1982). Placental transfer and metabolism of 17 alpha-ethynylestradiol-17 beta and estradiol-17 beta in the rhesus monkey. *Journal of Pharmacology and Experimental Therapeutics* **223**, 483–489.

Smith, L. L. & Hines, M. (2000). Language lateralization and handedness in women prenatally exposed to diethylstilbestrol (DES). *Psychoneuroendocrinology* **25**, 497–512.

Tehard, B., Kaaks, R. & Clavel-Chapelon, F. (2005). Body silhouette, menstrual function at adolescence and breast cancer risk in the E3N cohort study. *British Journal of Cancer* **92**, 2042–2048.

Titus-Ernstoff, L., Perez, K., Hatch, E. E., Troisi, R., Palmer, J. R., Hartge, P., Hyer, M., Kaufman, R., Adam, E., Strohsnitter, W., Noller, K., Pickett, K. E. & Hoover, R. (2003). Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology* **14**, 155–160.

Verdoux, H. (2002). Long-term psychiatric and behavioural consequences of prenatal exposure to psychoactive drugs [in French]. *Therapie* **57**, 181–185.

Verdoux, H. (2004). Perinatal risk factors for schizophrenia: how specific are they? *Current Psychiatry Reports* **6**, 162–167.

Verdoux, H., Geddes, J., Takei, N., Lawrie, S., Bovet, P., Eagles, J., Heun, R., McCreadie, R., McNeil, T., O'Callaghan, E., Stöber, G., Willinger, U., Wright, P. & Murray, R. (1997). Obstetric complications and age at onset in schizophrenia. An international collaborative meta-analysis of individual patient data. *American Journal of Psychiatry* **154**, 1220–1227.

Vessey, M. P., Fairweather, D. V., Norman-Smith, B. & Buckley, J. (1983). A randomized double-blind controlled trial of the value of stilboestrol therapy in pregnancy: long-term follow-up of mothers and their offspring. *British Journal of Obstetrics and Gynaecology* **90**, 1007–1017.

Watier, L., Richardson, S. & Hemon, D. (1997). Accounting for pregnancy dependence in epidemiologic studies of reproductive outcomes. *Epidemiology* **8**, 629–636.