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Association between fetal DES-exposure and psychiatric disorders in adolescence/adulthood: evidence from a French cohort of 1002 prenatally exposed children.

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Summary

In utero DES exposure has been demonstrated to be associated with somatic abnormalities in adult men and women. Conversely, the data are contradictory regarding the association with psychological or psychiatric disorders during adolescence and adulthood.

This work was designed to determine whether prenatal exposure to DES affects brain development and whether it is associated with psychiatric disorders in male and female adolescents and young adults. HHORAGES Association, a national patient support group, has assembled a cohort of ~~12820~~1282 women who took DES during pregnancy. We obtained questionnaire responses from 529 families, corresponding to 1182 children divided into three groups: Group 1 (n=180): firstborn children without DES treatment, Group 2 (n=740): exposed children, and Group 3 (n=262): children born after a previous pregnancy treated by DES.

No psychiatric disorders were reported in Group 1. In Group 2, the incidence of disorders was drastically elevated (83.8%), and in Group 3, the incidence was still elevated (6.1%) compared with the general population.

This work demonstrates that prenatal exposure to DES is associated with a high risk of psychiatric disorders in adolescence and adulthood.

Key words: Prenatal DES exposure, Psychiatric disorders, Suicide, Adolescence, Adulthood.

1. Introduction

From the 1950s to the late 1970s, millions of women took diethylstilbestrol (DES) during pregnancy to prevent miscarriages and premature births, to inhibit the milk inflow after childbirth, or to treat infertility, primary or secondary amenorrhea, dysmenorrhea and other genital disorders (Smith 1948). Strikingly, DES continued to be used despite various alerts that were published as early as 1940 (1) and the demonstration of Diekmann et al. (2) that DES was ineffective in preventing miscarriage or premature birth. In 1971, it emerged that *in utero* DES exposure was associated with somatic effects in adulthood, including female genital abnormalities (3,4), vaginal cancer (5), and male urogenital disorders (6). In experimental studies, mice exposed to DES during gestation were found to be more aggressive than controls (7), and the offspring of rats treated by intraperitoneal administration of another synthetic estrogen, ethinylestradiol (EE), were shown to present altered emotional states like anxiety and depressive-like behaviors (8,9). In humans, only three large epidemiological studies (10, 11, 12) and seven studies on a small number of exposed subjects (as summarized in the critical review of Kebir and Krebs) (13) have pointed out a risk of psychological or psychiatric disorders during adolescence or post-adolescence after *in utero* DES exposure. However, the data are discrepant (11) regarding the impact of DES on the developing fetal brain and the consequences for adolescents and adults. The aim of this work was to determine whether prenatal exposure to DES can induce psychological and/or psychiatric disorders in teenagers and young adults.

2. Materials and methods: The HHORAGES cohort

The HHORAGES Association (Halt to Synthetic Hormones for Pregnancies), a patient support group, has assembled a cohort of 1280 women who took DES during pregnancies. A detailed questionnaire (Table 1) was prepared and validated by researchers and doctors and sent to these families. As psychiatric diseases generally appear in the post-adolescent period, after 18 years, the

questionnaire concerned people born between 1946 and 1995. An authorization request was sent to the French "*Commission Nationale de l'Informatique et des Libertés*" (CNIL), which authorized the use of the questionnaire. We included items on patient sex, rank among siblings, specific exposure during gestation (DES alone or in association with EE), and somatic and psychiatric disorders.

Out of these 1280 families, 529 families responded to this extensive questionnaire, providing information on the family history; the mother's hormone treatment before and during pregnancy; medical records, including prescriptions; and the health problems of the children, including diagnoses and any medical treatments or hospitalizations. The psychiatric disorders reported in the questionnaires were classified as: eating disorders, behavioral disorders, obsessive-compulsive disorders, depression and bipolar disorders, schizophrenia, and suicides (attempts, death). When suicides or suicide attempts were reported, a second questionnaire validated by members of the Research Group on Suicide (CHU Lapeyronie Montpellier) was sent to the families.

3. Results

The results are presented in Table 2.

We collected completed questionnaires from 529 families, corresponding to 1182 children. Among these 1182 children, 180 firstborn children without DES exposure served as intra-familial controls (Table 2). The analysis was conducted according to specific descriptive criteria: treatment by synthetic xenohormones (DES, EE), exposed and unexposed children, patient sex, birth order rank, and somatic and psychiatric disorders.

Of the 1182 children (552 sons + 630 daughters) born from 529 mothers, we noted that 180 of them (102 sons + 78 daughters) were born without any DES exposure, before a DES-exposed pregnancy. We named this group "Pre-DES" (**Group 1**). 740 children (315 boys + 405

daughters + 20 stillborn) were born after DES exposition, this synthetic estrogen (banned only in 1977 in France) having been prescribed alone or in combination with ethinylestradiol (EE), we called this group “DES exposed” (**Group 2**). The third group was composed of the 262 children (130 sons + 132 daughters) born from a mother that had taken DES for a previous pregnancy: we named this group “Post-DES” (**Group 3**) (Table 2). In total, 1002 children were exposed (740 children exposed under prescription plus 262 Post-DES children, i.e., born after a previous pregnancy treated with DES).

In the exposed and post-DES children (**Group 2: n=740 – 20 stillborns + Group 3: n=262, for a total of 982**) we found that 603 children from Group 2 (250 sons + 353 daughters) and 16 from Group 3 were affected by psychiatric disorders (Table 2), in addition to 81 children with genital malformation and/or sterility but no apparent psychiatric disorders. In Group 2, 70 children were without any disorder and in Group 3, 242 children were without disorder.

For the 250 boys, psychiatric disorders were determined on the basis of family testimonies or medical records of antipsychotic or antidepressant prescription and/or psychiatric hospitalization, as follows: behavioral disorders, violence, aggressiveness, and obsessive-compulsive disorders (n=47), eating disorders (n=6), schizophrenia (n=112), and depression, bipolar disorder and anxiety (n=85), with schizophrenia being the most prevalent pathology. For the 353 girls, psychiatric disorders were as follows: behavioral disorders and obsessive-compulsive disorders (n=62), eating disorders (n=75), schizophrenia (n=53), and recurrent depressive or bipolar disorders (n=163), with affective disorders being the most prevalent.

Among the 262 post-DES cases, 16 of them (6.1%) presented psychiatric disorders and only four presented somatic disorders (4 girls). Among the 16 subjects presenting psychiatric disorders, one suffered behavioral disorders, six presented schizophrenia (3 boys + 3 girls), and

nine presented bipolar disorders and depression (3 boys + 6 girls); among them, one suicide and five suicide attempt series were noted.

From the 1182 children of our cohort, 180 firstborns were unexposed (102 firstborn boys + 78 firstborn girls): none of these firstborns presented any disorders, had ever made a suicide attempt or had committed suicide. Conversely, among the 982 exposed and post-DES children (1002 minus the 20 stillborns), we noted 33 suicides (24 sons + 9 daughters) and 107 series of suicide attempts (42 sons + 65 daughters), a series comprising between two and 15 suicide attempts per person. Thus, if we assume that the mean number of suicide attempts was six per person, about 642 suicide attempts were made (Table 3). The psychological and/or psychiatric disorders are presented in Table 4 along with the prevalences for these disorders in the general population (14, 15).

4. Discussion

Very few studies have investigated the impact of prenatal exposure to DES or synthetic hormones on psychiatric outcome. Up to now, most of the studies have been carried out on rodents and have shown the toxic effects of synthetic estrogens on the descendants, particularly in terms of behavioral disorders, as well as other effects like cancers (16), with multigenerational carcinogenic effects in mice (17). Injection of 17-alpha-ethinyloestradiol (EE) in pregnant rats induces not only a high rate of abortion, but also anxiety and depression-type disorders in pups (8,9). Based on these findings, it is hypothesized that estrogenic hormones induce neurodevelopmental disturbances in exposed human subjects and may potentially mediate an increased risk of behavioral and psychiatric disorders. Although selection biases (family association) may somewhat affect the impact of our data, the high prevalence of psychiatric disorders in the exposed subjects is quite striking, and it should be noted that the intra-familial controls were completely without disease. Our data therefore clearly demonstrate that DES

exposure during pregnancy is associated with a strikingly high incidence of behavioral and/or psychiatric disorders.

The prevalence of eating disorders in our cohort was eight times higher in the exposed adolescents and young women, as previously shown in a study of Gustavson et al., who reported on 1711 women with an OR of 5.72 (18). Behavioral disorders (11.2%) were also higher in the exposed population. Depression was four times-, 26.2%) more prevalent than in the general population, with the DES daughters being more affected than the sons. This observation confirms the epidemiological study from O'Reilly et al. (12). This group reported an OR of 1.47 in a group of 1612 exposed DES daughters. Our data also agree with the findings of Vessey et al. (10), who showed that the offspring of the exposed group -had twice as much anxiety as the offspring of the unexposed group. Several small case-control studies have since confirmed these findings (19-23), all reporting rates of major depressive disorders (MDD) significantly higher than for the general population. Our data illustrate a higher risk of schizophrenia, as this disease was 17 times more prevalent than in the general population, with sons being more affected than DES daughters. To date, there have been few data regarding this association. In 1987, Katz et al. (24) for the first time reported four subjects in a very small cohort suffering from psychosis after DES exposure; in 1993, Pillard et al. (23) observed several subjects in another cohort showing "paranoid ideation" (the diagnostic term today being "paranoid schizophrenia"). More recently, Kebir and Krebs (unpublished data in 13) analyzed the data from a small HHORAGES cohort and noted the high frequency of psychotic disorders but claimed that this finding did not demonstrate any causality between *in utero* DES exposure and a specific disorder. Nevertheless, these authors also examined three epidemiological studies with worldwide cohorts and several smaller cohorts with the objective of determining the impact of DES on the development of psychiatric disorders, including schizophrenia (13). They found that out of all these studies, only one did not support the hypothesis of a causal link (11). With regard to suicides, our work

clearly demonstrates a drastically increased risk of suicide attempts (65.4% *versus* 0 in the unexposed controls and 0.25% in general population) and suicides (3.4% *versus* 0 in the unexposed controls and 0.02% in general population). It could be noted that, as in the general population, DES sons commit more suicides than DES daughters, and inversely for suicide attempts. Moreover, our data reveal that 50% of the sons who committed suicide suffered from schizophrenia. Psychiatric studies in general have shown that the percentage of suicides is generally higher in individuals with psychiatric disorders than in the general population. But to our knowledge, there is no information or specific studies concerning this association in the context of DES exposure.

Sixteen subjects in Group 3 (post-DES children) (Table 2) had diagnosed psychiatric disorders. An explanation for this finding might be that DES-, being very lipophilic synthetic estrogens, remains in the mothers' fat after estrogenic impregnation in a previous pregnancy and are then released through the placental barrier in the next gestation.

5. Conclusion

In conclusion, we demonstrate here that prenatal exposure to DES is associated with psychiatric disorders in adolescence and adulthood. These data have been supported by recent preliminary work by Réseau DES-France suggesting a higher risk of psychiatric disorders in DES daughters, based on an analysis of the data from 3436 DES daughters *versus* 3256 control women (25). Moreover, in a recent review on the risk of psychiatric disorders in adolescents exposed *in utero* to DES, Kebir and Krebs (13), in agreement with Abdmalecky et al. (26), noted that the role of prenatal exposure to DES as an environmental factor for psychiatric disorders may involve a gene-environment interaction, as well as an epigenetic mechanism. This latter group reported for the first time that prenatal exposure to DES induced specific modifications in fetal

DNA methylation that could be involved in postnatal neurodevelopment and the subsequent psychiatric disorders in adolescence (27).

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Legends:

Tables:

<p><u>Mothers' situation</u> : Surname, First Name, Date of Birth, Address, Home phone number, Professional phone number, Mobile number, E-mail address</p> <p>Family Situation, Number of children, children's first names and dates of birth. Professional situation.</p> <p><u>Pill taken: before first pregnancy, and between pregnancies</u></p> <p><u>Hormonal treatment before pregnancy (or pregnancies). (If a treatment was prescribed, please indicate the nature of the treatment and the time elapsed between the end of treatment and the beginning of the pregnancy)</u></p> <p><u>Miscarriage(s): Indicate the time when it occurred, in relation to the other full term pregnancies, if any (before the first one, or between two full term pregnancies?)</u></p> <p><u>Professional Exposure to hormones, to chemicals (pesticides, etc...)</u></p> <p><u>Psychiatric or psychopathological family history (father, mother, .). Health problems after first child birth</u></p> <p><u>Pregnancy and childbirth (For more than 2 children, T.O.P.) 1st child, 2nd child..</u></p> <p><u>Treatment during pregnancy: (Yes/No) - Nature of medicines - Doses – What time during pregnancy (first and last day of treatment, expressed in weeks from the beginning of pregnancy)?</u></p> <p><u>What medical reason was put forward (possible miscarriage, comfort, etc...)? At what month did the delivery occur, from the start of the pregnancy?</u></p> <p><u>General condition of the child, Sex, Weight, Health problems at birth (mother and child) Existing documents (prescriptions, medical files, etc...) and testimonies</u></p> <p><u>Would you be so kind as to send us the copies of the files and documents? If yes, in order to save time, please attach the copies of all relative documents in your possession.</u></p> <p><u>Health problems of your children (For more than 2 children, T. OP)</u></p> <p><u>1st child, 2nd child First name, Sex, Birth Date, Rank in the sibling order Physical disorders: Which ones? What age? Sterility treatment? Surgery?</u></p> <p><u>Psychological disorders: Nature of first symptoms? What age? Subsequent aggravation? And at what age?</u></p> <p><u>Other data: Hospitalization, Violence, Suicide attempt(s), Medical Treatments, Diagnosis, AAH, Disability?</u></p> <p><u>Relational difficulties: in married life, in professional life?</u></p> <p><u>Children, grandchildren: How many? Full term? Health condition? Malformations or observed disorders?</u></p>

Table 1. Questionnaire sent to families.

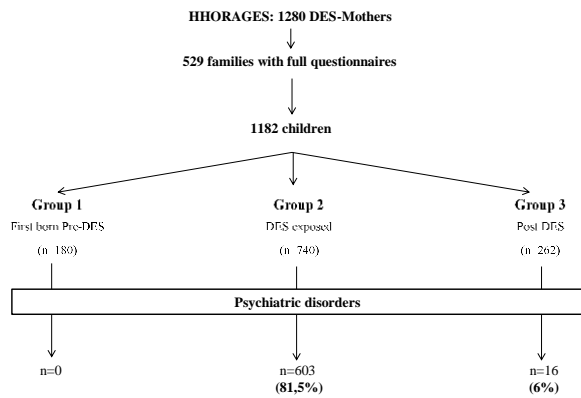


Table 2

Table 2. Classification of the three groups of the HHORAGES cohort.

Table 3 :

Among the 1002 DES exposed (Gpe 2)/ post exposed (Gpe 3) adolescents:

Behavioural disorders, violence, aggressiveness, obsessive compulsive disorders: n= 109	-----	(10,8%)
Eating disorders: n=81	-----	(8%)
Schizophrenia: n=165	-----	(16,5%)
Depression, bipolar disorder, anxiety: n=248	-----	(24,7%)
Suicides: n=33	-----	(3,3%)
Suicides attempts: n=642	-----	(64%)

Table 3

Table 3 : Total number of psychological/psychiatric disorders among the 982 (1002-20 stillborn) DES-exposed and post-DES children.

Table 4 :

	Group 2 DES exposed (n=740)	Group 3 Post DES (n=262)	Group 1 First born Pre-DES (controls) (n=180)	General population
Behavioural disorders	(14,7%)	(0,38%)	(0%)	(3%)
Eating disorders	(10,9%)	(0,76%)	(0%)	(1,6%)
Schizophrenia	(21,5%)	(2,3%)	(0%)	(1%)
Depression	(32,3%)	(3,4%)	(0%)	(6,3%)
Suicides:				
- attempts:	(82,7%)	(18,5%)	(0%)	(0,25%)
- death:	(4,3%)	(0,6%)	(0%)	(0,02%)

Table 4

Table 4: Prevalence of the psychological and/or psychiatric disorders and comparison with the general population.

Table 1. Questionnaire sent to families
