In utero exposure to diethylstilbestrol (DES): psychiatric disorders

Two French studies, including a case series, have investigated psychological or psychiatric disorders in hundreds of persons who were exposed to *diethylstilbestrol* in utero ("DES daughters" and "DES sons"). They show an increased frequency of psychiatric disorders such as schizophrenia, depression, and suicide attempts.

In utero exposure to *diethylstilbestrol* (*DES*) results in a variety of harmful effects, including long-term harms (1).

The data available in 2011 suggested an association between in utero exposure to *DES* and an increased risk of psychological disorders in adolescence or adulthood (2). The disorders described in these "DES daughters" and "DES sons" included depression, anorexia and bulimia (2).

This article summarises the main findings of our literature search to determine whether any more is known about this risk as of late 2017.

DES study in France: psychiatric disorders twice as common. The results of a study conducted by the action group *Réseau DES France* on psychiatric disorders in DES daughters were published in 2017. The 2566 questionnaires completed by DES daughters were compared with 2967 questionnaires completed by women aged 36 to 63 years who had not been exposed to *DES* in utero (control group) (1,3).

About 26% (679) of the DES daughters reported that they had experienced a severe mental health disorder or had consulted a psychiatrist, versus 16% (487) in the control group. After adjusting for various confounding factors, the odds ratio (a measure of relative risk) of psychiatric disorders after in utero *DES* exposure was 1.8 (95% confidence interval: 1.5-2.0). DES daughters were more likely than women in the control group to have a history of infertility, nulliparity, spontaneous abortion, fetal death or cancer. However, DES daughters and unexposed controls who had faced one or more of these difficulties were equally likely to have consulted a psychiatrist (3).

These results are consistent with those of 3 large epidemiological studies reported in *Prescrire* in 2011 (2).

Several hundred accounts. In 2016, HHorages (*Halte aux HORmones Artificielles pour les GrossesseS*), a French patient support group with a particular interest in the psychiatric disorders associated with in utero exposure to synthetic hormones, published an analysis of the responses to questionnaires provided by 529 women who had taken *DES* during pregnancy. The questionnaires focused on the health of a total of 1182 sons or daughters (4).

In the group of 720 DES children, psychiatric disorders were reported in 603 children (250 DES sons and 353 DES daughters), including 32 suicides. In the group of 262 children whose mother had taken *DES* during a previous pregnancy but not during their intrauterine period, psychiatric disorders were reported for 16 children, including one suicide. Among 180 children born before the mother was exposed to *DES* and who acted as controls, none were reported to have psychological disorders.

Recruitment through a patient support group is likely to overestimate the frequency of disorders. Nevertheless, these data provide an insight into the types of psychiatric disorders observed in exposed children.

The psychiatric disorders diagnosed and then reported for the 250 DES sons were: schizophrenia (112 cases); depression, bipolar disorder, anxiety (85 cases); behavioural disorders, violence, aggressiveness and obsessive-compulsive disorder (47 cases); and eating disorders (6 cases). Half of the DES sons who had committed suicide were reported to have schizophrenia.

The psychiatric disorders reported for the 353 DES daughters were: depression and bipolar disorder (163 cases); eating disorders (75 cases); behavioural disorders and obsessive-compulsive disorder (62 cases); and schizophrenia (53 cases) (4).

In practice Although outcomes reported by DES daughters and mothers exposed to *DES* during pregnancy provide only weak evidence, these accounts are consistent with the epidemiological data.

Taken together, the evidence makes a plausible case for a psychological component to the long-term harms of exposure to *DES* during pregnancy.

The long-term consequences of in utero exposure to *DES* are a very strong argument for evaluating the long-term effects of in utero exposure to synthetic hormones and more generally to other pharmaceutical and non-pharmaceutical substances.

Translated from *Rev Prescrire* **February 2018**
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Prescrire's literature search up to 23 November 2017

1- Prescrire Editorial Staff "Diethylstilbestrol (DES): also harms the third generation" *Prescrire Int* 2016; **25** (177): 294-298.

2- Prescrire Editorial Staff "Psychological consequences of DES exposure in utero" *Prescrire Int* 2011; **20** (121): 264-266.

3- Verdoux H et al. "Impact of prenatal exposure to diethylstilbestrol (DES) on psychological outcome: a national survey of DES daughters and unexposed controls" *Arch Womens Ment Health* 2017; **20**: 389-395.

4- Soyer-Gobillard MO et al. "Association between fetal DES-exposure and psychiatric disorders in adolescence/adulthood: evidence from a French cohort of 1002 prenatally exposed children" *Gynecol Endocrinol* 2016; **32** (1): 25-29.