



Diethylstilbestrol and autism

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It is acknowledged that diethylstilbestrol (DES), a synthetic diphenol with powerful estrogenic properties, causes structural anomalies of the reproductive tract and increases the risk of cancer and genital malformations in children and grandchildren of mothers treated during pregnancy. Conversely, data on DES effects on neurodevelopment and psychiatric disorders in *in-utero* exposed children and their descendants are rare, especially concerning Autism Spectrum Disorders (ASD). Recent studies presented in this review strengthen the hypothesis that *in-utero* exposure to DES and also other synthetic estrogens and progestogens, which all are endocrine disruptors, contributes to the pathogenesis of psychiatric disorders, especially ASD. A large epidemiological study in the USA in 2010 reported severe depression in *in-utero* exposed children (n=1,612), and a French cohort study (n=1,002 *in-utero* DES exposed children) in 2016 found mainly bipolar disorders, schizophrenia, major depression, suicide attempts, and suicide. Few publications described ASD in *in-utero* exposed children, mainly a Danish cohort study and a large Chinese epidemiological study. Molecular studies on endocrine disruptors demonstrated the transgenerational induction of diseases and DES epigenetic impact (DNA methylation changes) at two genes implicated in neurodevelopment (*ZFP57* and *ADAM TS9*). We recently described in an informative family, somatic and psychiatric disorders in four generations, particularly ASD in boys of the third and fourth generation. These data show that the principle of precaution must be retained for the protection of future generations: women (pregnant or not) should be extremely vigilant about synthetic hormones.

KEYWORDS

diethylstilbestrol, psychiatric disorders, autism, epigenetics, endocrine disruptors

Introduction

Diethylstilbestrol (DES), a synthetic diphenol with powerful estrogenic properties, is considered the culprit of many somatic disorders in children and grandchildren of mothers treated during pregnancy (1). It has been estimated that worldwide, ~10 million people have been exposed to DES (2). However, very few studies investigated DES effects on neurodevelopment and psychiatric disorder occurrence, especially Autism Spectrum Disorders (ASD), in exposed children and their descendants. A previous review that included a small number of epidemiological studies reported inconclusive results on the risk of psychiatric disorders in DES-exposed individuals (3). On the other hand, O'Reilly et al. (4) analyzed data from a large US epidemiological study (the Nurses' Health Study), on 76,240 American women among whom 1,612 were exposed to DES *in utero*. They found that the occurrence of major depressive and anxiety disorders was significantly increased (by a factor of 1.47) in exposed women. Two other studies reported psychiatric effects, particularly schizophrenia, bipolar disorders, depression, eating disorders, suicide attempts, and suicide, in adolescent/adults who were *in-utero* exposed to DES (5, 6) and to progestins (7).

In humans, ASD, a neurodevelopmental disorder, is characterized by impaired social interaction, language and communication and also stereotypical behavior (8). In the last years, several studies have brought insights into ASD genetics (9) and epigenetics (10); however, very few works have investigated the relationship between ASD and *in-utero* exposure to synthetic estrogens and/or progestins. Specifically, Zou et al. (11) demonstrated that in rats, prenatal exposure to levonorgestrel (LNG; a synthetic progestin used in oral contraceptive pills) inhibits estrogen receptor ER β expression in the amygdala through increased methylation of its promoter. ER β downregulation led to decreased expression of superoxide dismutase 2 and estrogen-related receptor α , and subsequently triggered damage in amygdala tissue through oxidative stress and dysfunction of mitochondria and fatty acid metabolism. These effects contributed to the autism-like behavior observed in the *in-utero* exposed offspring. This suggests that upon LNG exposure, ER β downregulation in the amygdala during

neurodevelopment may contribute to autism-like behavior. Similarly, Li et al. (12) in a large study on a human population found that prenatal progestin exposure was associated with ASD (see section 1.3). According to Perrotti (13), ERs and progesterone receptors (PRs) function as ligand-dependent transcription factors and their distinctive transcriptional activities are initiated when they bind to their respective ligands, like other members of the nuclear hormone receptor superfamily. The ER and PR signaling pathways are modulated through epigenetic mechanisms.

In recent decades, ASD prevalence has significantly increased. This indicates that besides heritability and genetic background, other factors might be implicated in these disorders, particularly environmental factors that influence the central nervous system (CNS) development. Several toxic compounds have been linked to ASD risk, such as heavy metals, air pollutants, pesticides, polycyclic aromatic hydrocarbons and polybrominated diphenyl ethers. In this review, we present studies suggesting that exposure to DES and other synthetic sexual hormones also might contribute to the increasing ASD prevalence.

Methods

A systematic review of the literature was carried out by searching the PubMed and Google Scholar databases for the period from 2010 to 2022 following the PRISMA guidelines. The chosen starting year was 2010 because it was the year of publication of the study by Titus-Ernstoff et al. (14) showing for the first time DES multigenerational effect in humans, although it only concerned somatic disorders. Only the study by Colborn published in 2004 (15) was added, as a tribute. Studies were identified using the following keywords: diethylstilbestrol, diethylstilbestrol and ASD, progestins, progestins and ASD, psychosis and endocrine disrupting compounds, estrogens and epigenetics. Publications that were not articles (e.g. conference abstracts) and publications that were not in English were excluded.

Psychiatric disorders in children *in-utero* exposed to DES

Although DES has not been administered to pregnant women since 1971 (USA) and 1977 (France), it continues to wreak havoc in the subsequent generations. Moreover, it was replaced by ethinylestradiol (EE), which cannot be used during pregnancy since 1980, and by synthetic progestins that are still marketed with EE, particularly in contraceptive pills. Synthetic hormones, such as DES, EE, synthetic progestins, were prescribed often as a cocktail not only to women who had a

Abbreviations: *ADAM TS9* gene, Implicated in the control of organ shape (uterus and reproductive organs) and CNS development; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Syndrome Disorders; DES, Diethylstilbestrol; DSD, Disorders of Sex Development; DMR, Differentially Methylated Region; EE, Ethinylestradiol; ER β , Estrogen Receptor β ; CpG, Cytosine near Guanine; LNG, Levonorgestrel (a progestogen); Progestins, Synthetic forms of the body naturally-occurring hormone progesterone; ZFP57, Gene located on chromosome 6 and expressed very early in development. It is a transcription regulator, directly related to methylation and neurodevelopment.

miscarriage or were at risk of miscarriage, but also to those in discomfort or even as a “morning after pill”.

The database of the families of the French patient association Hhorages-France allowed assessing the causal link between *in-utero* exposure to synthetic hormones, particularly DES, and the occurrence of severe psychotic disorders after adolescence in exposed children. This database is based on the responses to a detailed questionnaire written by physicians and researchers and approved by the French national commission for data protection and freedom (CNIL) (7). In 2016, we analyzed data on 1,182 pregnancies from 529 mothers from the Hhorages-France cohort (Table 1). We found that 603/720 children exposed to DES *in-utero* and 16 post-DES children (i.e. born after a previous exposed pregnancy but without *in utero* exposure) had psychiatric disorders, but none of the 180 children born before the pregnancy with DES treatment. Compared with the

general population, the prevalence of psychiatric disorders in this group was significantly increased (Table 1b) (5). Other synthetic hormones, such as EE and progestogens, also are implicated. For instance, *in-utero* exposure to estrogens or progestins increases the risk of bipolar disorders/depression and schizophrenia (Figure 1) (16, 17). Patients with bipolar disorder or depression often present also eating disorders (bulimia, anorexia) (Table 1). In the Hhorages cohort (5), 30% of children *in-utero* exposed to DES had eating disorders (n =83 vs n=257 with bipolar depression, depression, or anxiety disorder alone). This high rate suggests a possible endocrine cause for this pathology the vulnerability factors of which are still incompletely known (18). Similar observations were reported also in other studies (in the general population) where eating disorders were often associated with major depressive disorders (19, 20). Specifically, Liu et al. (21)

TABLE 1 Effects of synthetic estrogens (DES, EE) on psychiatric disorders *in-utero* exposed children (2nd generation).

529 families with completed questionnaires		
1182 children		
First born unexposed	DES exposed	Post-DES
n=180	n=720	n=262
Psychiatric disorders		
n=0	n=603 (83.8%)	n=16 (6.1%)
	(353 girls, 250 boys)	
b Psychiatric disorders in DES-exposed (n=603) and post-DES adolescents (n=16)		General population
Behavioral disorders, violence, aggressiveness, obsessive-compulsive disorders n=110	(11.2%)	(3%)
Eating disorders (n= 83)	(8.4%)	(1.6%)
Schizophrenia (n= 171)	(17.4%)	(1%)
Depression, bipolar disorder, anxiety (n=257)	(26.2%)	(6.3%)
Suicide (n= 33)	(3.4%)	(0.02%)
Suicide attempts (n= 642)	(65.4%)	(0.3%)

(a) Total number of psychological/psychiatric disorders among the 982 DES/EE-exposed and post-DES unexposed children. The first unexposed children (n= 180) were used as intrafamilial control. With permission by Taylor & Francis Ltd (www.tandfonline.com). (b) Psychiatric disorder rate among the 982DES/EE *in-utero* exposed and post-DES children and in the general population. Note the particularly high number of suicides and suicide attempts. With permission by Taylor & Francis Ltd (www.tandfonline.com).

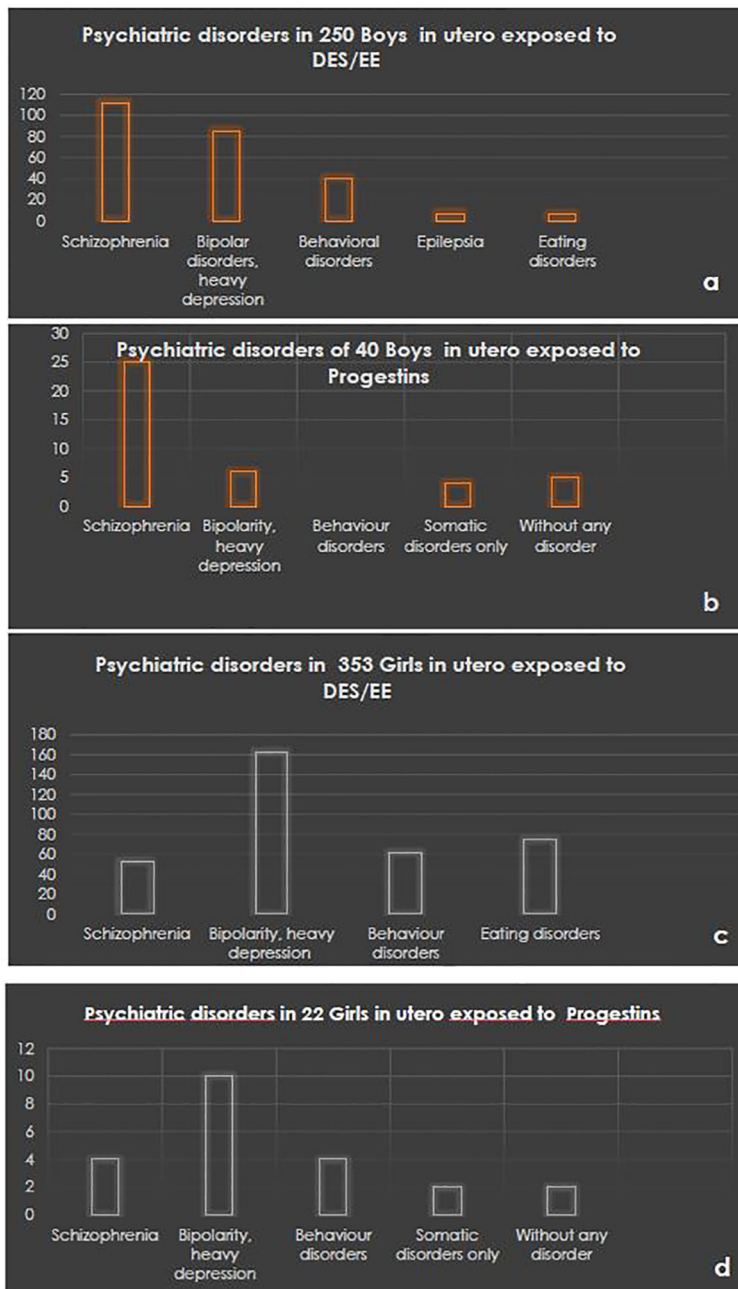


FIGURE 1 Psychiatric disorder rates in boys *in-utero* exposed to DES/EE (A) or to progestins (B) and in girls exposed to DES/EE (C) or to progestins (D). ©Hhorages-France data.

carried out a genome-wide association study in which they compared genomic data on 184 patients with bipolar disorder comorbid with eating disorders, 1,370 healthy controls, and 2,006 patients with bipolar disorder only. They found a genome-wide association of eating disorders and bipolar disorders and confirmed the association of the *SOX2-OT* gene

with bipolar disorders comorbid with eating disorders. Regions containing genes involved in neurodevelopment were also associated with this group. Moreover, Remnelius et al. (22), Carpita et al. (23), Saure et al. (24), Westwood et al. (25) reported a link between ASD and anorexia nervosa, and suggested a specific genetic link between anorexia nervosa and ASD.

TABLE 2 Progesterin exposure and ASD: An epidemiological study in a large Chinese population.

Impact factors	No. of cases (n = 235)	No. of controls (n = 682)	Statistic (χ^2 value)	P value
Family History of Mental Diseases	23	56	0.551 (df = 1)	0.458
Preterm birth (<37 weeks)	25	57	1.1161 (df = 1)	0.291
Birth Asphyxia	34	74	2.2011 (df = 1)	0.138
Paternal Age			0.8841 (df = 2)	0.643
<20 years	12	36		
21–34 years	184	550		
>34 years	39	96		
Maternal Age (year)			10.8691 (df = 2)	0.004*
<20 years	21	47		
21–34 years	145	498		
>34 years	69	137		
Paternal Personality			0.4021 (df = 2)	0.818
Extroverted	30	79		
Middle	150	450		
Introverted	55	153		
Maternal Personality			0.3061 (df = 2)	0.858
Extroverted	39	110		
Middle	145	412		
Introverted	51	160		
Major Stressful Life Event #	26	56	1.7471 (df = 1)	0.186
Paternal Smoking and Areca Chewing History	112	281	2.9761 (df = 1)	0.085
Maternal Abortion History	51	121	1.7991 (df = 1)	0.180
Use of Progesterin to Prevent Threatened Abortion #	36	51	12.5141 (df = 1)	0.000*
Use of Progesterin Contraceptives at the Time of Conception	26	41	6.5871 (df = 1)	0.010*
Prenatal Consumption of Progesterin-Contaminated Seafood (g/week)			38.7781 (df = 2)	0.000*
100–400	69	359		
400–800	92	191		
800–1,200	74	132		

*, indicates significant difference; #, during the first trimester of pregnancy; df, degrees of freedom.

a

b

Impact factors	β	SE	Wald χ^2	P value	Odds ratio (95% CI)
Maternal Age (21–34 years (Ref))			12.373	0.002*	
<20 years	0.640	0.471	1.841	0.175	1.527(0.209–2.329)
>34 years	2.605	0.775	11.913	0.001*	2.074(1.017–2.324)
Paternal Smoking and Areca Chewing History	1.317	0.778	2.867	0.090	3.733 (0.813–17.151)
→ Use of Progesterin to Prevent Threatened Abortion #	2.863	0.537	24.925	0.000*	14.631 (5.103–41.952)
→ Use of Progesterin Contraceptives at the Time of Conception	2.756	0.371	55.234	0.000*	15.743 (7.610–32.568)
→ Prenatal Consumption of Progesterin-Contaminated Seafood (g/week) (100–400 (Ref))			85.948	0.000*	
400–800	3.593	0.395	82.187	0.000*	35.998 (16.589–78.115)
800–1,200	4.643	0.631	54.067	0.000*	103.863 (30.128–358.057)

*, indicates significant differences; #, during the first trimester of pregnancy; df, degrees of freedom

(a) Potential impact factors of progesterin exposure for ASD in a Chinese population-based case-control study. The three major exposure sources during pregnancy are indicated with black arrows. ©Li et al. (12). (b) Multivariate regression analysis of the impact factors on ASD prevalence after progesterin *in-utero* exposure. Note the high odds ratio for the three major progesterin exposure sources (black arrows). ©Li et al. (12). With permission.

Estrogen impact on neurodevelopment: Epigenetic alterations that can be transmitted to the subsequent generations

Data and families from the Hhorages-France cohort were used also to study the molecular basis of the causal link between *in-utero* exposure to synthetic estrogens and the appearance of psychotic disorders, such as schizophrenia and bipolar disorders (26). From this cohort, 69 siblings (n=37 *in-utero* exposed to DES: 12 boys and 25 girls; and n=32 unexposed: 12 boys and 20 girls) from 30 families were selected for DNA methylation analysis in peripheral blood samples. This analysis highlighted specific differences in DNA methylation at the *ZFP57* and *ADAMTS9* genes between exposed and unexposed participants that were correlated with psychotic disorders, particularly schizophrenia, depression and bipolar disorders. In this pioneering work, the authors analyzed the methylation variations of 411,947 CpG sites/per genome in peripheral blood samples, because it was previously reported that the methylation profiles in brain and blood samples are rather similar (27). Controls were unexposed elders (“informative family”) and another cohort of unexposed adolescents who became schizophrenic and were followed at St. Anne Hospital, Paris (28). On the basis of these results, the authors suggested that in exposed individuals, psychosis is associated with specific methylome modifications (i.e. hyper methylation) that modify the gene activity and consequently could influence neurodevelopment and neuroplasticity. One of the genes in which methylation changes have been observed is *ADAMTS9* that encodes a disintegrin and metalloproteinase with thrombospondin motifs 9 (*ADAMTS9*). Members of the *ADAMTS* family of proteoglycanases have been implicated in proteoglycan cleavage, organ shape control during development, and angiogenesis inhibition (29, 30). Specifically, sexual organ shape alteration, which is often observed in children *in-utero* exposed to DES, is caused by deregulation of procollagen N-proteinases of the *ADAMTS* family that regulate collagen fibril assembly and of aggrecanases, other *ADAMTS* members that regulate the cleavage of extracellular matrix proteoglycans, thus modifying the extracellular matrix structure and function. In addition, the aberrant activation of *ADAMTS9* could induce premature rupture of gestational membranes before the end of gestation (31). Moreover, Tokmak et al. (32) and Wan et al. (33) suggested a link between *ADAMTS9* and endometriosis. Therefore, deregulated expression of *ADAMTS* proteoglycanases might influence fetal neuroplasticity by affecting the extracellular matrix structure and function in nervous system cells (34, 35).

Estrogens and progestogens may induce autism spectrum disorders

Baron-Cohen et al. (36) analyzed by liquid chromatography and mass spectrometry analysis amniotic fluid samples from 128 boys with ASD from the Danish Historic Birth Cohort. They found (36) that the fetal concentrations of sex hormones (especially progesterone and 17- α -hydroxyprogesterone) were elevated compared with matched control and provided the first evidence of increased fetal steroidogenic activity in autism. Using the same cohort and methods, the authors analyzed the prenatal levels of estrogens and progesterone in the amniotic fluid of boys with (n=98) and without autism (n=177). They observed that the prenatal estrogen and progesterone concentrations were higher in amniotic fluid of boys who developed autism. They concluded that prenatal estrogen alterations influence brain development and sexual differentiation and also contribute to the risk of autism.

Biochemical and molecular studies using limbic tissues from the offspring of progestin-injected pregnant rats (11) showed that prenatal progestin exposure induces autism-like behavior in the offspring through estrogen receptor β (ER β) suppression in the brain, suggesting that progestin may be implicated in ASD development. Specifically, pregnant rats received LNG alone, LNG plus EE, or EE alone from day 1 to day 21 of gestation. Half of the offspring was used for *in vivo* behavioral studies and the other half for cytochemical, immunological and biochemical studies of the dissected limbic compartment (amygdala, hippocampus and hypothalamus). The authors found that both LNG and LNG/EE significantly increased DNA methylation at the ER β promoter in amygdala neurons from 10-week-old male and female offspring.

These results in an animal model were then confirmed in a large case-control epidemiological study (Table 2) showing the association of prenatal progestin exposure with ASD (12). The authors investigated a large population in Hainan, an island of 8 million people in southern China. Among 37,863 children (0–6 years of age), they selected 235 children with ASD and 682 matched controls. They observed that the following mother-related factors were strongly associated with ASD prevalence: use of progestin to prevent abortion (15.3%), use of progestin contraceptives at conception time (11%), and prenatal consumption of progestin-contaminated seafood during the first trimester of pregnancy (all mothers). The association with the consumption of contaminated seafood by mothers is particularly striking. Indeed, according to the authors, currently in China, combined oral contraceptives are widely used by the seafood industry for pregnancy prevention in fish and shrimps because they can grow faster and become fatter if they do not lay eggs. This may partly explain the increasing incidence of ASD in China (and in other countries). Therefore, pregnant women must be especially careful and must avoid

eating oral contraceptive-contaminated seafood. To confirm these findings, the authors gave to pregnant rats synthetic progesterin (norethindrone)-treated zebrafish as food, and found that their offspring showed autism-like behavior. The authors concluded that prenatal progesterin exposure may be associated with ASD development.

DES, autism and multi- and trans-generational effects

In a large multi-center study on prenatal DES exposure, Titus-Ernstoff et al. (14) observed somatic defects among 4,029 sons (genitourinary anomalies, risk of infertility and testicular cancer) and 3,808 daughters (infertility, reproductive tract anomalies, pregnancy loss, premature delivery, vaginal clear cell adenocarcinoma, risk of breast and cervical cancer) who were *in-utero* exposed. Moreover, for the first time, they reported birth defects in the offspring of prenatally exposed and unexposed children. They also reported the first molecular studies in female mice showing that exposure to DES results in epigenetic alterations.

In 2011, using data on 529 families from the Hhorages-France cohort, Kalfa et al. (37) found that the percentage of children with hypospadias was more than doubled in the grandsons compared with the sons of women who took DES during pregnancy (8.2% vs 3.5%), showing DES multigenerational effect on genital malformations. Rivollier et al. (26) also proposed a possible transgenerational epigenetic effect. These findings confirm the work by Skinner's group (38) on the epigenetic transmission of the alterations caused by endocrine disruptors and on the epigenetic transgenerational inheritance of diseases. More recently, in a cohort study on DES-linked neurodevelopmental effects that included 47,540 women spanning three generations, Kioumourtoglou et al. (39) reported attention-deficit/

hyperactivity disorder (ADHD) in the third generation of children. ADHD etiology involves a combination of genetic and environmental risk factors. The authors concluded that "DES exposure is associated with multigenerational neurodevelopmental disorders". Similarly, Gaspari et al. (40, 41) described DES effects on somatic disorders in grandchildren (i.e. primary clear cell carcinoma of the cervix in an 8-year-old granddaughter and endometriosis in granddaughters and possibly one great-granddaughter). Recently, we described in an informative family of 11 children (the elder not exposed was the control), the impact of DES prescribed to suppress lactation for 3 months on the children born after such treatment and their progeny (genealogic tree of this informative family in Figure 2), by focusing on psychiatric disorders (bipolar disorders, suicide attempts and suicide, eating disorders) (42, 43). These psychiatric disorders were associated with somatic disorders, such as endometriosis and hypospadias (Table 3). Importantly, in the third generation, 10/19 DES-exposed grandchildren had psychiatric disorders, especially ASD, Asperger syndrome or ASD without Asperger syndrome (in boys) and bipolar disorders for girls, associated with dyspraxia and learning disabilities, mood and behavioral disorders and eating disorders, as well as somatic comorbidities. In the fourth generation (n=7 DES-exposed great-grandchildren, aged between 0 and 18 years), one child had dyspraxia and ASD. In the family of the non-exposed daughter, no psychiatric or somatic disorders were reported (Figure 2 and Table 3).

There are very few studies on the multigenerational (and likely transgenerational) effects of DES in human diseases. It has been hypothesized that ASD originate *in utero* due to molecular perturbations of the developing brain. Ladd-Acosta et al. (44) in a pilot post-mortem study found that *ZFP57* is more methylated in cerebellar tissue samples of women with autism than unrelated controls. In Sprague-Dawley rats, Zou et al. (11) detected DNA hypermethylation on the promoter of the gene encoding ER β in the

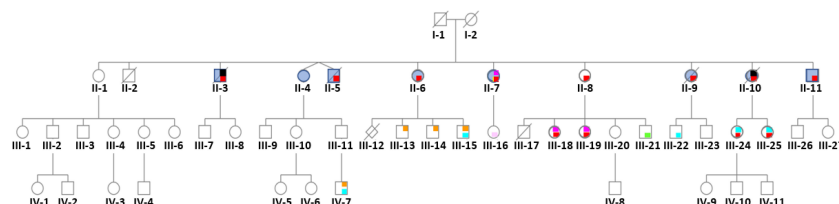


FIGURE 2

Pedigree of an informative family where the mother (I-2) was treated with DES (30 mg/day) for 3 months after each delivery to inhibit lactation. Only the first child (II-1) was not exposed to DES *in utero*. Daughter II-1 and her descendants do not have any psychiatric disorder. No history of psychiatric disorders was reported for the maternal and paternal sides. red = bipolar disorder, yellow = psychosis borderline, blue = attempted suicide(s), black = suicide, orange = autism spectrum disorder, light blue = dyspraxia and learning disabilities, light pink = mood and sleep disorders, green = behavioral disorders, fuchsia = eating disorders. ©Soyer-Gobillard et al. (42) IJERPH, 18, 9965, MDPI.

TABLE 3 Psychiatric disorders (columns 2 and 3) and comorbidities (column 4) in the four generations of an informative family (column 1) whose mother (first generation) took DES for 3 months after each delivery (see Figure 2).

Patient	Psychiatric disorder	Diagnosis	Associated non-psychiatric disorders	Suicide attempt(s)	Death by suicide
II-1 ♀	no	no	no	no	no
II-2 ♂	no	no	Uvula bifida, death due to ruptured congenital brain aneurysm at 26 years of age	no	no
II-3 ♂	yes	Bipolar disorder, chronic alcoholism	Deafness of left ear	yes	yes (at 42 years of age)
II-4 (♀ twin)	yes	Eating disorder	Endometriosis	no	no
II-5 (♂ twin)	yes	Bipolar disorder, chronic alcoholism	Chronic cirrhosis death at 51 years of age	yes	no
II-6 ♀	yes	Bipolar disorder	Endometriosis, inverted kidney/bladder	yes	no
II-7 ♀	yes	Bipolar disorder, chronic alcoholism, eating disorder	Endometriosis, sacrococcygial teratoma, rectal adenocarcinoma, breast cancer	yes	no
II-8 ♀	yes	Bipolar disorder, chronic alcoholism	Endometriosis, fibromyalgia, obesity	yes	no
II-9 ♀	yes	Bipolar disorder, chronic alcoholism	Endometriosis	yes	no
II-10 ♀	yes	Bipolar disorder, chronic alcoholism	Endometriosis	yes	yes (at 50 years of age)
II-11 ♂	yes	Bipolar disorder, chronic alcoholism	no	yes	no
III-1 ♀	no	no	no	no	no
III-2 ♂	no	no	no	no	no
III-3 ♂	no	no	no	no	no
III-4 ♀	no	no	no	no	no
III-5 ♀	no	no	no	no	no
III-6 ♀	no	no	no	no	no
III-7 ♂	no	no	no	no	no
III-8 ♀	no	no	no	no	no
III-9 ♂	no	no	no	no	no
III-10 ♀	no	no	Endometriosis	no	no
III-11 ♂	no	no	Hypospadias	no	no
III-12 ♂	/	Very premature baby, anencephaly, deceased	/	/	/
III-13 ♂	X	ASD, Asperger syndrome	Hypospadias	no	no
III-14 ♂	X	ASD, Asperger syndrome	no	no	no
III-15 ♂	X	ASD, learning disorder (dyspraxia)	no	no	no
III-16 ♀	X	Mood and sleep disorders	Endometriosis	no	no
III-17 ♂	/	Very premature baby, (deceased at day 3 post-partum)	/	/	/
III-18 ♀	X	Bipolar disorder, eating disorders	Endometriosis	no	no
III-19 ♀	X	Bipolar disorder, eating disorders	Endometriosis	no	no
III-20 ♀	no	no	Endometriosis	no	no
III-21 ♂	X	Behavioral disorders	no	no	no
III-22 ♂	X	Learning disorder (dyspraxia)	no	no	no
III-23 ♂	no	no	no	no	no
III-24 ♀	X	Bipolar disorder, learning disorder	Endometriosis	no	no
III-25 ♀	X	Bipolar disorder, learning disorder	Endometriosis	no	no
III-26 ♂	no	no	no	no	no
III-27 ♀	no	no	no	no	no
IV-1 ♀	no	no	no	no	no
IV-2 ♂	/	/	/	/	/

(Continued)

TABLE 3 Continued

Patient	Psychiatric disorder	Diagnosis	Associated non-psychiatric disorders	Suicide attempt(s)	Death by suicide
IV-3 ♀	no	no	no	no	no
IV-4 ♂	/	no	no	no	no
IV-5 ♀	no	no	no	no	no
IV-6 ♀	no	no	no	no	no
IV-7 ♂	yes	ASD, learning disorder (dyspraxia)	no	no	no
IV-8 ♂	/	/	/	/	/
IV-9 ♀	/	/	/	/	/
IV-10 ♂	/	/	/	/	/
IV-11 ♂	/	/	/	/	/

amygdala of the offspring *in-utero* exposed to LNG alone or the LNG/EE combination. Interestingly, this effect was less important in female than male rats, as observed also in humans, in agreement with our own recent observations in four generations (42) (Figure 2; Table 3). In a post-mortem study, Corley et al. (45) showed significant DNA methylation defects in the brain, supporting the hypothesis of an early developmental origin of ASD. In our recent works (42, 46), we confirmed the findings by Kiourmoutzoglou et al. (39) on the multi-generational and very probably trans-generational impact of DES on neurodevelopment. This strengthens the hypothesis that *in-utero* exposure to DES (and to other endocrine disruptors) contributes to the pathogenesis of psychiatric disorders, particularly autistic disorders (47, 48). According to the theory proposed by Nilsson and Skinner (49), epigenetic alterations (epimutations) induced by environmental insults (e.g. exposure to toxicants) and their transgenerational (germline-mediated) inheritance increase disease susceptibility. Indeed, besides the pregnant mother (F0 generation) who is directly exposed to the insult, also the fetus (F1) and its germline are exposed (Figure 1) (50). These exposed germ cells will give rise to the F2 generation (grandchildren). Therefore, the first generation without direct environmental exposure is the F3 generation (great-grandchildren). The F3 generation may exhibit transgenerational inheritance of disease susceptibility. Several epimutations can be implicated in this non-genetic inheritance (48): DNA and RNA methylation changes, histone modification alterations, non-coding RNAs and extracellular vesicles. It has been already shown that upon DES exposure, the *ZFP57* and *ADAMTS9* genes become hypermethylated. More studies are needed to identify other epimutations linked to *in-utero* exposure to DES.

Concomitant neurodevelopmental disorders and genital malformations

Concomitant neurodevelopmental impairment and male genital malformations (disorders of sex development, DSD) have been observed in children exposed *in utero* to DES. Chen

et al. (51) reported that boys with cryptorchidism were more likely to receive a diagnosis of ASD (HR 1.24). Similarly, using nation-wide Israeli healthcare data, Rotem et al. (52) highlighted a correlation between male genital malformations and ASD (odds ratio of 1.62) (52). The authors suggested that prenatal androgen defects could be implicated in ASD etiology. We identified several girls and boys with concomitant ASD and DSD in the Hhorages-France cohort (preliminary data) (Table 3). Moreover, Bodur et al. (53) recently reported that among 432 boys with ASD, 4.4% had a genital abnormality. Similarly, Pham et al. (54) reviewed data on 447 male children with ASD. They detected genital malformations in 68.5% of them, a much higher rate than previously reported.

Key findings on DES effects from this review

- Psychiatric effects of estrogens and progestins *in-utero* exposed children were analyzed using data from a French cohort. Comparisons of groups exposed to different synthetic progestins or estrogens (DES, EE) revealed that the frequency of psychiatric disorders (schizophrenia, bipolarity, eating disorders) is the same whatever the drug.
- A study on the molecular mechanism of estrogen action in the brain of *in-utero* exposed children showed that psychosis was correlated with specific methylome modifications (hypermethylation) in two genes implicated in the neurodevelopment, thus highlighting an epigenetic mechanism.
- Progestin may contribute to ASD development *via* an epigenetic mechanism (hypermethylation of the ER β gene promoter in the amygdala). A large Chinese epidemiological study showed that many mothers of

children with ASD were treated or contaminated by progestins and by oral contraceptive components during pregnancy.

- Analysis of the amniotic fluid in a Danish cohort of boys that included also children with ASD showed that prenatal exposure to estrogens, or other prenatal sex steroids (e.g. progestins) contributes to autism.
- A multigenerational and possibly transgenerational effect of DES on neurodevelopment and psychiatric disorders had been observed, especially for ASD.

Conclusions

All these results, particularly those reported by Zou et al. (11) and Li et al. (12), support the hypothesis formulated by Kim Strifert (55, 56) on the link between oral contraceptives and higher ASD risk in children (in 2015, 1 in 68 (56) vs in 2018, 1 in 44 children (57) were diagnosed with ASD in the USA. Strifert hypothesized that the estrogen and progestogen used in oral contraceptives act as endocrine disruptors. Specifically, they may affect germ cells/oocytes and give rise to a potent risk factor that helps to explain the recent increase in ASD prevalence. Moreover, such synthetic hormones might cause epigenetic changes. For instance, EE, a known endocrine disruptor, may trigger DNA methylation of the ER β gene, leading to its downregulation and impaired estrogen signaling in the progeny brain. In 2015, Strifert hypothesized also that the deleterious effects of estrogens and progestogens could be transgenerational.

Therefore, in the absence of large-scale epidemiological studies, the principle of precaution must be imperatively retained for the protection of the future generations: pregnant or not, women should be extremely vigilant about any kind of synthetic hormone therapy. In 2004, the great biologist and epidemiologist T.E. Colborn wrote (15): “The fetus can be protected from endocrine disruptors, whatever they are, only at the zero dose”.

Author's note

Association HHORAGES-France, a patient association, is registered at the Epidemiological Portal of French Health Databases INSERM (French National Institute for Medical Research) and AVIESAN (National Alliance for Life Sciences and Health) (epidemiologiefrance.aviesan.fr).

Author contributions

M-OS-G. drafting the manuscript; LG, PC and CS: revising the manuscript critically for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

M-OS-G is a researcher, president of the HHORAGES-France Association and a mother concerned with DES and other synthetic hormones.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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