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Chapter

Evidence for Link Between Mental Disorders and in Utero Exposure to Synthetic Hormones: A Long and Crucial History

Marie-Odile Soyer-Gobillard, Laura Gaspari and Charles Sultan

Abstract

Somatic effects of diethylstilbestrol on children exposed in utero have long been recognized. This is not the case for psychiatric disorders, although animal studies provide evidence of somatic and behavioral disorders. Recent studies have reported psychiatric effects of synthetic estrogens on the brain of children exposed in utero as schizophrenia, bipolar disorders, depression, eating disorders, suicides, suicide attempts. Recently, a team of St. Anne's Hospital, Paris (Prof. Krebs, Dr. Kebir) demonstrated the epigenetic mechanism of DES effect on the brain, a specific methylation of two genes playing important roles in neurodevelopment: the ADAM TS9 (control of the formation of reproductive organs and of the fetus's CNS) and the ZFP 57 gene suggested to be associated with psychosis. Progestins used in contraception and in hormone replacement therapy are known to affect the adult brain, but no data on children existed before our recent paper on their effects after in utero exposure. Clinical data were collected from 1934 children of the Association of Patients HHORAGES cohort. Our data show the presence of somatic disorders and a drastic increase of psychiatric disorders among children in utero exposed to progestins. These mental disorders are the same as pathologies provoked by exposure to synthetic estrogens.

Keywords: synthetic estrogens, diethylstilbestrol, ethinyl estradiol, synthetic progestins, mental disorders, in utero exposure

1. Introduction

At the end of the 1990s, somewhere in France, an agricultural engineer, Mr. RA, made the observation that his three children were suffering from various psychic and somatic pathologies, the elder suffering from bilateral cryptorchidism, micropenis, infertility due to azoospermia (no spermatozoa), and schizotypal character; the second from anxiety, depression, and eating disorders (anorexia) coupled with small uterus and ovaries; and the third suffering from

schizophrenia and severe depression associated with suicide attempts. He observed also the relationship with the fact that in all three cases, his wife received medical treatment consisting of a synthetic hormone cocktail: diethylstilbestrol (DES), ethinyl estradiol (EE), plus synthetic progestin delay during her three pregnancies after a previous miscarriage. He conducted research in the world literature on the subject and came to the conclusion that not only was one of these products, diethylstilbestrol (DES), already known for its misdeeds but that it continued to be administered in France until 1977/1982. The product, inexpensive to make, was not patented and was manufactured and distributed by many pharmaceutical laboratories. The same goes for EE, which was banned for pregnant women in 1980 but remains the best-selling estrogen in the world because it is part of the contraceptive pill.

In 1998, one of us (MOS-G), concerned by the same kind of problems in her two children who were exposed in utero to the same cocktail of synthetic estrogens, lost her two children after psychiatric illnesses. Following the reading of a "Call to Families" printed in a newspaper, she met Mr. RA, who had gathered around him about 20 French families concerned with their in utero-exposed children suffering from psychiatric illnesses. He wanted to expose his observations and the results of his bibliographic researches at a meeting of patient families collecting observations on the genital malformations of girls exposed in utero to DES. Alas, he was condemned, rejected, and disclaimed by doctors, mostly gynecologists and psychiatrists as well as by associative members. They denied the existence of psychiatric disorders in exposed boys and girls. Discouraged, Mr. RA died shortly afterward. In order to continue his work and regroup the families concerned by the origin of the heavy psychiatric pathologies of their children and despite the taboo surrounding such diseases as psychoses, we gathered several mothers concerned and created the Association of Patients Halt to Artificial Hormones for Pregnancies (HHORAGES), in 2002. This Association which collected more than 1300 French spontaneous testimonies is now registered with the Epidemiology Portal of French National Institute for Medical Research (INSERM) as a French Health Database.

Despite various alerts published in the 1940s, after work on animals proving in particular its carcinogenic effect, and despite the work of Dieckman et al. [1], initiated as early as 1953, demonstrating in a large cohort of pregnant women given diethylstilbetrol (DES), a synthetic estrogen, *versus placebo* that the drug was inefficient in preventing miscarriages or premature births, this product has been widely distributed around the world, sowing a long list of misdeeds. After the discovery of cervicovaginal cancers called "clear cells adenoma (CCAD)" [2] in the "DES girls," DES was banned in the United States for pregnant women in 1971 but only in 1977 in France, where this recommendation disappeared from the "French Vidal book," but DES continued to be prescribed sporadically until 1982. Meanwhile another synthetic estrogen, steroidal, also synthesized on 1938, 17-alpha-ethinyl estradiol (EE), was often added to DES as a cocktail or later as a replacement, sometimes with the addition of synthetic-delay progestin. The idea that prevailed at the time was that women had a hormonal deficit that triggered a miscarriage, whereas now we know that the miscarriage itself causes this deficiency. These products were prescribed not only to women who had miscarriages but also in comfort ("to have beautiful babies," according to an advertising) or even as a "morning after pill" or to cut milk after childbirth. DES and 17-alpha-EE, although belonging to different estrogenic and degrading categories, are, however, bound to the same ER beta-estrogen receptors.

2. Behavioral disorders demonstrated in animals (rats) exposed in utero

Animal studies (on mice and rats) have demonstrated the toxicity of these synthetic estrogens on the offspring, including the cause of behavioral disorders [3–8]. Palanza et al. [3] demonstrated in particular that prenatal exposure to three different synthetic chemicals, DES and two pesticides, DDT and methoxychlor, and its analog, affects the behavior of young suckling mice, showing increased aggression in males (increased numbers of attacks and decreased reaction time before the attack) (**Figure 1**). Doses of DES were 1000 times less than those of DDT and caused much larger aggression responses, demonstrating the considerable effect of DES at very low doses. The treatment period for rodent mothers from day 11 to day 17 of pregnancy was also critical because it represents a key period in the differentiation of the reproductive system and brain development in these rodents in the early stages of pregnancy.

Moreover, injection of 17-alpha-estradiol (EE) in pregnant rats causes not only many abortions in mothers but also anxiety and depression disorders in offspring [4, 5], the synthetic hormone having been administered at the same relative doses as in humans (15 g/kg, 1 per day, versus 19 g/kg, 1 per day). At the cytological level of the brain, an alteration of the anterior part of the hippocampus in young rats exposed to EE in utero has been demonstrated in 2004 [6]. The hippocampus is indeed a part of the brain that contains many estrogen receptors during the prenatal period. Ogiue-Ikeda et al. [7] showed in 2008 that synaptic plasticity can

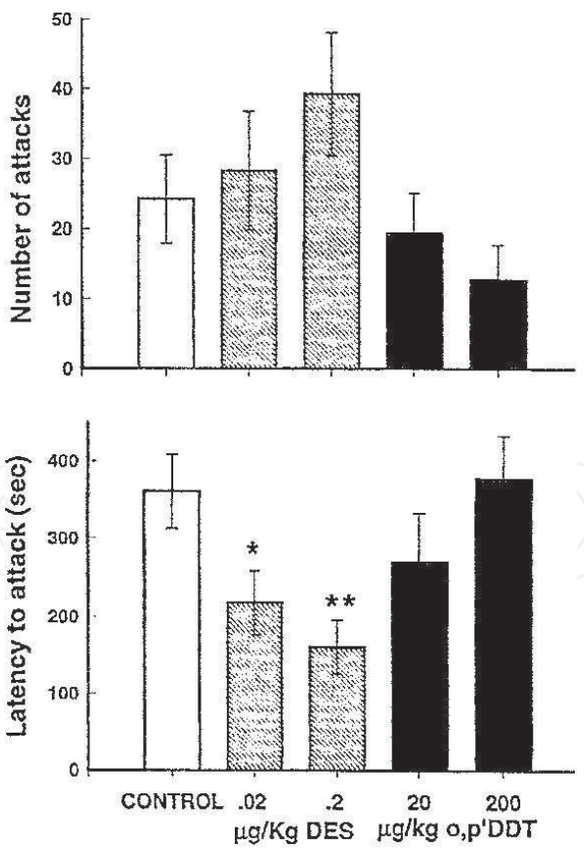

Figure 1.
Measurement of aggressiveness in young male mice after prenatal exposure to diethylstilbestrol (DES) (0.02 and 0.2 µg/kg) [in gray], DDT [20 and 200 µg/kg] [in black], with a control without DES [in white]. There is an increase in the number of attacks and a decrease of the reaction time before the attack although the doses of DES are 1000 times less than those of DDT. According to Palanza et al. [3], with the permission of Elsevier (License No: 2514671323242).

be upset by estrogens or other endocrine disruptors (EDs). Later and unequivocally, Newbold demonstrated the validity of the rodent model transposed to humans [8].

3. Behavioral disorders, psychoses, and depression demonstrated in humans after in utero exposure to DES/EE

In humans, the work concerning the appearance of behavioral disorders in children after in utero exposure to synthetic hormones is less numerous, but as early as 1977, June Reinisch [9] published in Nature that prenatal exposure to estrogen and/or synthetic progestins could affect the personality of exposed children. More recently, in 2012, Kebir and Krebs [10] have analyzed several epidemiological studies concerning the effects of DES on exposed children in utero and the occurrence of psychiatric disorders in these children. Their analysis shows that only three large epidemiological studies on the effects of DES were performed in 1952–1953 (followed up in 1983), in 2007, and in 2010. The first study (double-blinded) that supports the hypothesis of a link between psychiatric disorders and prenatal exposure to DES was performed by Vessey et al., in 1983 [11], from a clinical trial that had been performed 30 years earlier in 1953 in London by Dieckman et al., on 700 women treated with DES versus 700 subjected to a placebo [1]. A doubling of depression and anxiety disorders has been demonstrated in the population exposed in utero. The second, published in 2007 and conducted by Verdoux et al. [12], from a cohort of women from the Mutuelle (Health) de l'Education Nationale (MGEN) concludes that there are no significant links between exposure to DES, suicides, and/or psychiatric consultations or hospitalizations. A detailed analysis later, however, revealed a number of biases in this study [13]. The most recent Nurses' Health Study was conducted by O'Reilly et al., 2010 [14], from 76,240 American women among whom 1612 women were exposed to DES in utero. The statistical analysis shows that the latter experienced an increase in depressive and anxiety disorders by a factor of 1.3. Kebir and Krebs [10] emphasized the limitations of such epidemiological studies and noted in particular that, apart from depression and anxiety, other psychiatric disorders have not been studied. Postadolescence behavioral disturbances reported for these two estrogens in exposed children were depression [15, 16], anxiety [1, 11, 17], schizophrenia-like behavior [18, 19], anorexia, and bulimia nervosa [20]. All these observations were synthesized by Pillard et al. [16] and Giusti [21]. On 1987, Katz et al. [18] described the case of four male adults prenatally exposed to DES. It is in late adolescence that they develop psychotic disorders requiring neuroleptic treatment even though they have no family history of this type. He then hypothesizes that there may be a causal relationship between disruptions in neurodevelopment related to DES and the subsequent onset of psychotic disorders. Pillard et al. [16] showed that the frequency of recurrent major depressive episodes is significantly higher in the DES-exposed than in their unexposed siblings, which was confirmed in 2010 in the large cohort of DES girls by O'Reilly et al. [14].

Investigation of the causal link between exposure to these synthetic hormones in utero and severe psychotic disorders such as schizophrenia, bipolar disorders with or without eating disorders, and schizoaffective disorders, occurring in post-adolescence in exposed children, was made possible thanks to the families of the Association HHORAGES. Our database, constituted by these spontaneous families' testimonies, is based on responses to a detailed questionnaire, written by doctors

and researchers and accepted by the CNIL (French Center for the Protection of Data Processing and Freedom). Our first global analysis (2004–2005 data) was based on 967 pregnancies from 470 mothers in collaboration between 2 of us (MOS-G/CS) of us (CS). The first results as well as the family questionnaires were detailed in 2012 in the chapter published in 2012 by InTech "Behavioral and Somatic Disorders in Children Exposed In Utero to Synthetic Hormones" [13] in which we detailed somatic and psychiatric disorders, associated or not, in the exposed children of our cohort.

We have conducted a more recent analysis (2016) [22, 23] based on 1182 pregnancies from 529 mothers (**Figure 2**).

Among the 740 (20 stillborn) exposed children, 603 (exposed) +16 post-DES (born without exposure but after a previous exposed pregnancy) are suffering from psychiatric disorders. The prevalence of the psychiatric disorders in comparison with the general population shows a dramatic increase (**Table 1**).

We were also interested by the effects on the brain of synthetic progestins on in utero-exposed children of our cohort (**Figures 3** and **4**). Currently, there is no research on these effects of in utero exposure of children to progestins given alone during pregnancy. Our recent observations [24, 25] were collected from 1200 families of the HHORAGES cohort, that is, 1934 children using always the same detailed questionnaire [13]. As previously shown, most families of our cohort had children exposed to estrogens or to estro-progestins, but only 46 families (115 children) had at least 1 child exposed to 1 or more progestins prescribed alone and representing 62 in utero-exposed children. Thirty-five children were post-exposed (**Figure 3**). The prescribed progestins were 17-α-hydroxyprogesterone caproate (synthetic progestin, SP) against total indication in 2000 but reauthorized in 2011, 17-α-hydroxyprogesterone heptanoate (SP) against total indication in 2002, and chlormadinone acetate (SP), derived from hydroxyprogesterone, against total indication in 1970.

Among the 62 exposed children (22 girls and 40 boys), 49 presented psychiatric disorders, 6 presented somatic disorders only, and 7 did not present any disorder. Only 1 post-exposed presented psychiatric disorder, while 34 other post-exposed did not present any disorder.

Among the 49 children affected by psychiatric disorders, 3 boys and 7 girls presented both somatic disorders in addition to psychiatric ones: boys (3), hypospadias (1), no urinary meatus (1), bilateral cryptorchidia, and sexual ambiguity (1) and girls (7), hormonal sterility (2), hirsutism and enuresis (1), enuresis (1), hirsutism (1), hermaphrodism (1, operated), and sexual ambiguity and tight

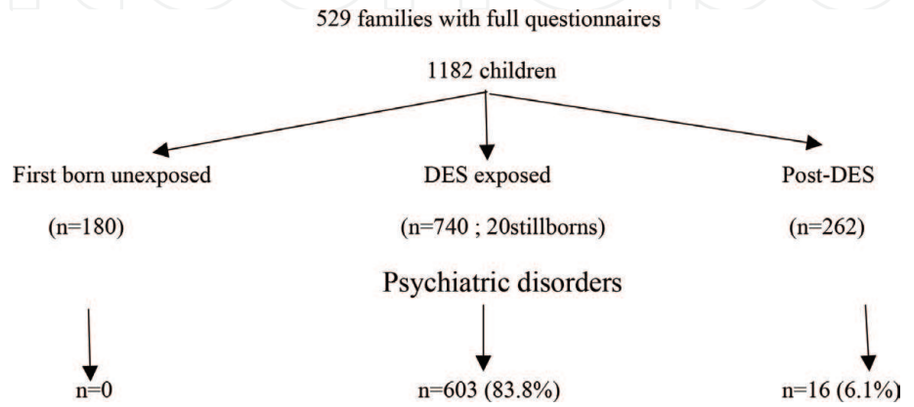

Figure 2.
Total number of psychological/psychiatric disorders among the 982 (1002 total with 20 stillborns) DES-exposed and post-DES unexposed children. First-born children (intrafamilial control) unexposed are not ill.

	Group 1	**Group 2**	**Group 3**	
	First-born pre-DES	DES-exposed	Post-DES	General population
	n = 180	n = 740-20	n = 262	
Behavioral disorders	0%	n = 109 (15.1%)	n = 1 (0.4%)	3%
Schizophrenia	0%	n = 165 (22.9%)	n = 6 (2.3%)	1%
Eating disorders	0%	n = 81 (11.3%)	n = 2 (0.8%)	1.6%
Depression				
Bipolar disorders, anxiety	0%	n = 248 (34.4%)	n = 9 (3.4%)	6.3%
Suicide attempts	0%	n = 612 (85%)	n = 30 (11.5%)	0.3%
Death	0%	n = 32 (4.4%)	n = 1 (0.4%)	0.02%

Table 1.
Prevalences of the psychological and/or psychiatric disorders in in utero-exposed children to DES and/or EE and comparison with the general population [23].

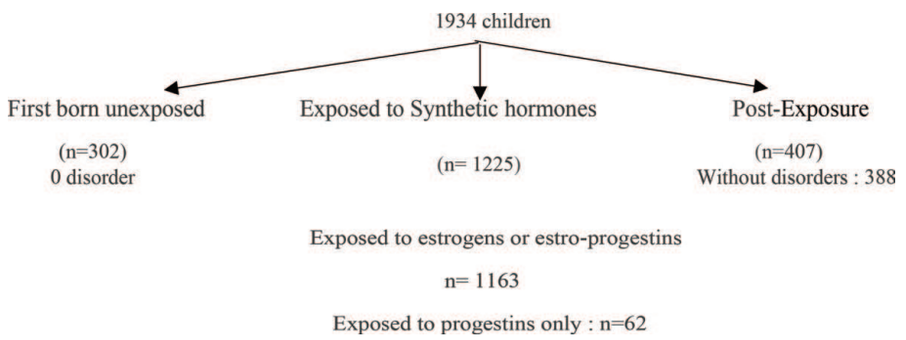

Figure 3.
Total HHORAGES cohort of 1934 children in which 3 groups can be observed.

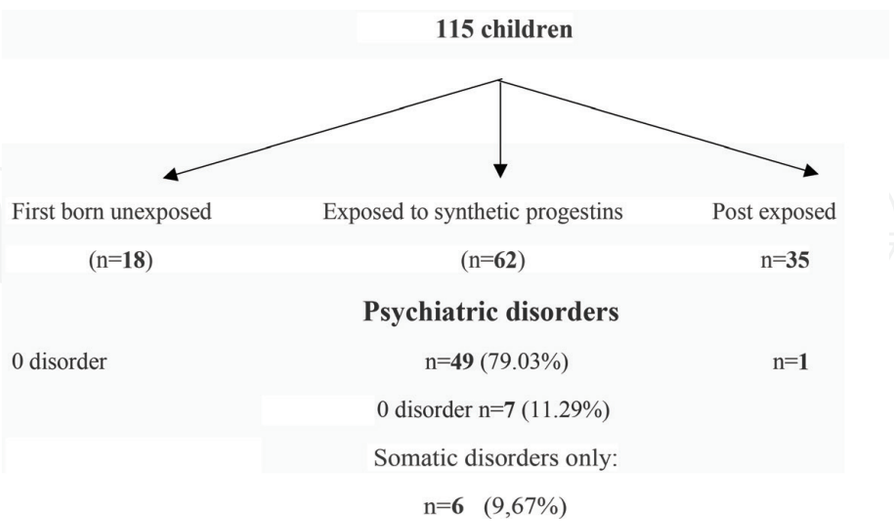

Figure 4.
Division of the 115 children of the 46 "progestins" families: first-born unexposed, in utero exposed, and post exposed, that is, born after a previous exposed pregnancy.

urethra (1). Among the six exposed children suffering from somatic disorders "only," we observed for boys (four) mega bilateral ureter (one grandchild), unilateral cryptorchidia (one), hypospadias with numerous interventions of

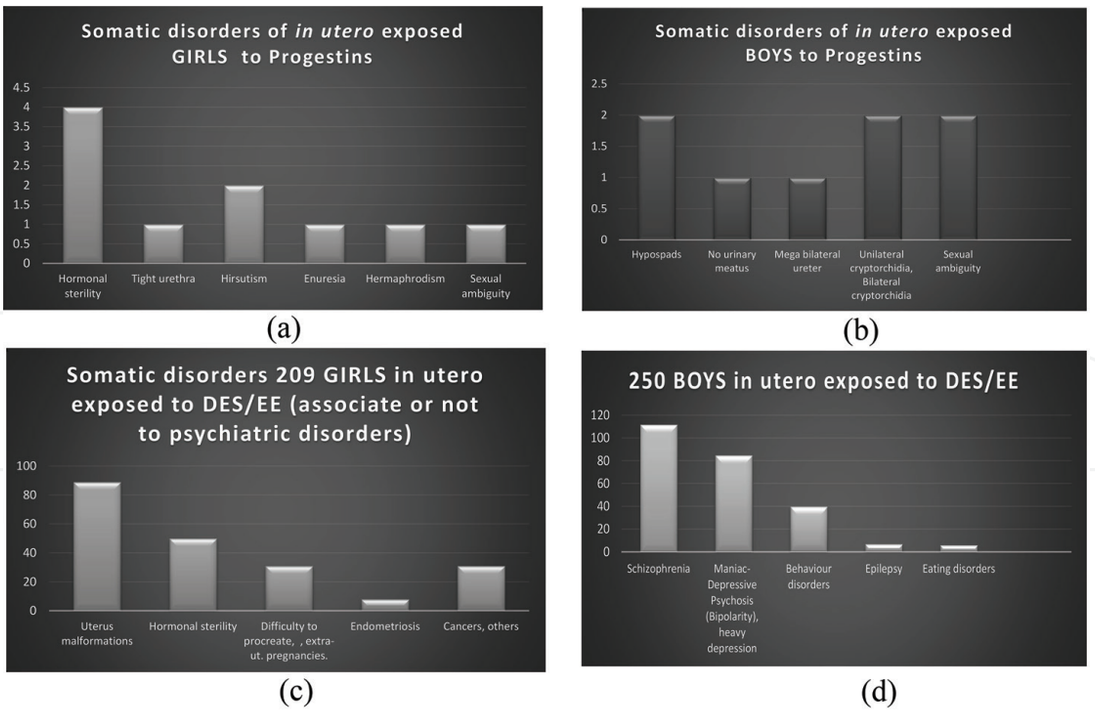

Figure 5.
Comparative diagrams representing psychiatric disorder cases presented, respectively, by girls (a, c) and boys (b, d) exposed either to synthetic estrogens diethylstilbestrol (DES) and ethinyl estradiol (EE) (c, d) or to synthetic progestins (a, b).

reconstruction (one grandchild), and sexual ambiguity (one) and for girls (two) hormonal sterility (two).

As shown in **Figure 5**, a comparison of synthetic estrogen and progestin exposures for girls and boys demonstrates that psychiatric disorders were of the same nature for progestin exposure as those observed after exposure to synthetic estrogens, that is, behavioral disorders = 2, eating disorders = 2, schizophrenia = 29, depression, bipolar disorders = 16, suicides attempts = 7 series, and death = 1. The percentage of suicide attempts (11.29%) and death after suicide (1.6%) is proportionately lower after exposure to progestins than after exposure to synthetic estrogens.

4. An epigenetic mechanism

Search for the molecular basis of the causal link between in utero, exposure to synthetic hormones and the appearance of psychoses as schizophrenia or bipolar disorder in children exposed in utero, has been achieved thanks to the partnership that unites HHORAGES Patients' Association with the INSERM team of molecular psychiatrist Pr. MO Krebs (St. Anne's Hospital, Paris, France, UMR S 894), which began in 2007. "It would have been 'crazy' to miss the problem posed by the Association Hhorages to establish a causal link between taking artificial hormone (s) during pregnancy and appearance of psychiatric disorders of the type psychotic in exposed children, because diethylstilbestrol (Distilbene® or DES) has been given over a limited period of time and people who have taken this molecule are still there to testify. This is a case study that should not be missed" said Dr. Kebir (Center for Psychiatry and Neuroscience, UMR S 894), manager of these researches as part of the Krebs' team.

First, to document in utero exposure to synthetic estrogens, Kebir and Krebs [10] were able to analyze from our data a small number of family records that occurred in HHORAGES testimonies and studied a cohort of 472 exposed subjects. They account for 46.7% of mood disorders, 22.9% of psychotic disorders, 6.6% of anxiety disorders, 11% of eating disorders, and 12.7% of others, which confirms their previous observations published on 2009 and 2010 at the seventh and eighth Congress of the Encephalon in Paris [26, 27] on 43 exposed children highlighting clinical pictures with atypical associations.

Second, genetic and epigenetic analyses of HHORAGES siblings have shown in patients suffering from psychotic disorders and exposed in utero to DES and/or EE that this prenatal exposure is associated with epigenetic processes. Starting from the fact that psychiatric diseases develop from a brain dysfunction during neurodevelopment, and knowing that DES and EE are synthetic hormones (estrogens), endocrine disruptors, and confirming from the HHORAGES data numerous cases of heavy psychiatric disorders in children exposed, the Krebs'team in association with HHORAGES designed 10 years ago, in 2007, a research project Partnership Citizen Institution for Research and Innovation (PICRI), funded by the Ile de France Region, net by the French National REsearch Agency (ANR), that developed the hypothesis that the DES administered during pregnancies could be an environmental risk factor for the development of psychiatric disorders in impregnated children: the epigenome of the foetus could have been modified by in utero exposure to synthetic estrogens. The PICRI project was titled "Influence of hormonal treatments on brain development during pregnancy: study of phenotypic, behavioral and biological changes in informative families." The families of HHORAGES were called to perform peripheral blood sampling after thorough questioning. Many families volunteered to participate in the research: 31 families were selected, satisfying the rigorous inclusion criteria desired. Many more families had come forward during this study, but they could not be included because the psychotic patient refused to come to St. Anne's Hospital for blood sampling. In the selected families, total siblings were composed of first-born unexposed children, exposed children, and post-exposed children, with first-born unexposed serving as intrafamilial control. For the exploration of their epigenome, 485,000 cytosines by genome were studied and analyzed, representing an immense work. To complete this study, a cohort of young adolescents with relational, emotional, and social difficulties was followed for 6 months, some of whom had developed schizophrenic-type psychosis in these 6 months, although not exposed to DES. A comparison of their methylome, analyzed before and after the onset of the disease, was performed. In this study [28], authors reported a global methylation of the psychotic patient genome.

After the analysis of the whole methylome of the selected HHORAGES cohort, the team of Krebs-Kebir highlighted differential specific methylated regions (DMR): in the zinc finger protein 57 gene ZFP57 and in the ADAM TS9gene and in young psychotic patients exposed in utero to DES/EE [29, 30]. In this work, the authors observed that in exposed individuals, ZFP57 gene methylation may be associated with their psychosis. The ZFP57 gene (located on chromosome 6) is expressed very early in development. It is a transcription regulator, directly related to the phenomenon of methylation and neurodevelopment [31]. The ADAM TS9 gene is implicated in the control of organ shape, especially in the development and function of the uterus and reproductive organs [32] which are often abnormal after in utero DES exposure as well as in the control of the CNS development [33] and in several kinds of cancers [34].

5. Discussion and conclusion

Very few studies have investigated the impact of prenatal exposure to DES and EE on psychiatric outcome. Animal studies on rats or mice allowed us to hypothesize that estrogenic hormones induce neurodevelopmental disturbances in exposed human subjects and may potentially mediate an increased risk of behavioral and psychiatric disorders. Our data therefore strongly suggest that DES/EE exposure during pregnancy is associated with high incidence of behavioral and/or psychiatric disorders. They 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. Regarding the existence of eating disorders (bulimia, anorexia), it should be noted that girls are much more affected than boys, and we often observed the association of eating disorders with bipolarity (manic-depressive disorders), anxiety, and depression. 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 the general population) and suicides (3.4% versus 0 in the unexposed controls and 0.02% in the general population). It could be noted that, as in the general population, DES sons commit more suicides than DES daughters and the inverse 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) (**Figure 2** and **Table 1**) had diagnosed psychiatric disorders. An explanation for this finding might be that DES, being a very lipophilic synthetic estrogen, remains in the mothers' fat after estrogenic impregnation in a previous pregnancy and is then released through the placental barrier during the next gestation.

No work had been reported on the impact of in utero exposure to synthetic progestin hormones administered alone on the occurrence of psychiatric disorders in exposed children before our first presentation in the European Congress of Gynecology in 2017 [24]. For the first time, we described psychiatric disorders that can affect children exposed in utero to progestins. Previously, and during many years, synthetic progestogens were not considered as dangerous during pregnancy or during replacement or contraceptive treatment. Moreover, they have been suggested to exert neuroprotective effects in several animal models of neurological disease [35]. Negative mood symptoms have been reported by Andreen et al. [36] in some women as a result of progesterone during the luteal phase of menstrual cycles. This is believed to be mediated via the action of allopregnanolone on the GABA-A system. A reduction of allopregnanolone circulating levels that correlates to depressive symptoms has been recently reported [37], and conversely, healthy women reported increased anxiety and mood disorders after long-acting subdermal implant of progestogens. In a group of 236 schizophrenic patients at onset, an elevated concentration of progesterone has been found, and authors suggested that steroid hormones may influence brain function, underlying schizophrenia, and major depressive disorders [38]. Moreover, Buoli et al. (2016) found high DHAS levels in patients with a history of psychotic symptoms, suggesting a role of steroids in the etiology of psychosis and mood disorders [39]. Progestins are known to induce GABA receptor activity/neural activation before birth; it is likely that a GABAergic system could contribute to schizophrenia, anxiety, depression, panic disorders, epilepsy, autism, and others [40]. Although some progestins have been banned from the market, others are not: our data demonstrated that caution should

be taken with regard to the use of these progestins during pregnancy and even outside these periods (contraception or hormone replacement therapy).

The brain is a very vulnerable organ because its development covers a very broad period extending from the early prenatal stage (third week of pregnancy) to end around the age of 20. During its development, there are times when its vulnerability is even greater than others; these periods are called "shooting windows," during which the environment can impact the normal process of development. Abdolmaleky et al. [41] as early as 2005 had developed the hypothesis that gene-environment modulations could be performed via DNA methylations. Krebs' team put forward the hypothesis that DES-induced changes in epigenetic background and alteration of DNA functioning (methylations) could be significant factors to demonstrate a possible origin of psychotic disorders and a link with in utero DES exposure of the children suffering from these illnesses [29, 30].

Numerous studies have shown that, for example, in the rat, early maternal separation or the fact of causing significant stress to the mother changes the methylation signals of certain genes of the rat directly related to the regulation of anxiety. It has also been discovered that the proper environment for changing the methylation signals may be chemical. This is the case of DES recognized by the scientific community as an endocrine disruptor and banned for pregnant women. This change in the level of methylation caused in utero by DES has been demonstrated for urogenital malformations of girls and boys as well as for cancers. On 2015, Harlid et al. published in a pioneer work the first study for evaluation of possible effects of in utero DES exposure on genome-wide DNA methylation in humans [42]. They studied whole blood DNA methylation in 100 40–59-year-old women reporting in utero exposure, compared to 100 unexposed women. They did not find any differential methylation, but the DMR approach was not used in their recent work (2015). On the other hand, in 2017 Rivollier et al. [30] described specific differential methylated regions (DMR) on two genes implicated in neurodevelopment (ZFP57 and ADAMTS9). Surprisingly, they cautiously claim that these DMR are "supposedly" associated with prenatal exposure to DES in young psychotic patients in utero exposed to DES/EE. Nevertheless, these modifications of methylation are really specific because they do not exist in the methylome of young psychotic patients not exposed to DES [28] in which global methylation of the genome was observed. Moreover authors have compared exposed subjects to their unexposed siblings which do not present these specific methylations although they shared environmental and genetic factors.

The citizen work carried out between the French HHORAGES Patient Association and two major medical research laboratories has provided convincing scientific results: (1) on the detection and confirmation of the existence of psychiatric disorders (accompanied or not of somatic disorders) in children exposed in utero to synthetic hormones and (2) on the mechanisms of action of these synthetic hormones administered to pregnant mothers on the brain of their offspring. The effects of these endocrine disruptors in humans through what is becoming a public health scandal, denied for a long time by doctors, especially psychiatrists, scientists, and specialized journalists, are thus better known. The fact that these synthetic products do not degrade in the human body in the same way as the natural hormones [13] and act on the functioning of genes implicated in neurodevelopment during the fetal life, following an epigenetic mechanism, is a real time bomb. Indeed, this mechanism induces a transgenerational effect already partially demonstrated in the HHORAGES cohort at the third-generation level for hypospadias, a specific genital malformation. So far, only a few third-generation children suffering psychiatric illness are documented in the HHORAGES testimonies. This is understandable because third-generation exposed children are still too young (excepted in some cases) to present psychiatric disorders as schizophrenia which is not the case for hypospadias that are detectable

from birth in male children and grandchildren [43]. In contrast, psychiatric disorders usually appear in postadolescence, 18–20 years, and sometimes later.

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Notes

Association HHORAGES-France is registered on the Epidemiological Portal of French Health Databases INSERM (French National Institute for Medical Research) and AVIESAN (National Alliance for Life Sciences and Health) (epidemiologie-france.aviesan.fr).

Disclaimer

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