

Minireview**Consequences of In Utero Exposure to Synthetic Estrogens and Progestogens for Children**Marie Odile Soyer Gobillard^{1, 2}, Laura Gaspari³ and Charles Sultan⁴¹PH.D., Director of Research Emeritus, CNRS, Sorbonne Université, Observatoire Océanologique-Laboratoire Arago, Banyuls-sur-Mer, 66650, France.²HHORAGES-France Association (Stop Artificial HORMones for Pregnancies), 78 Av. Guynemer Perpignan, 66100, France.³M.D., Paediatric endocrinologist, Unité d'Endocrinologie-Gynécologie Pédiatrique, CHU Montpellier, University Montpellier, 34090 Montpellier, France.

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⁴M.D., PH.D. Professor Emeritus, Service de Pédiatrie, Unité d'Endocrinologie-Gynécologie Pédiatrique, CHU Montpellier, University Montpellier, 34090 Montpellier, France.**Abstract**

Synthetic estrogens and progestogens have been administered for decades to millions of pregnant women around the world to prevent miscarriages or for comfort. We are actually discovering that psychiatric disorders can affect not only children exposed in utero, but also grandchildren and likely grandgrandchildren whether or not associated with genital malformations or other somatic disorders. Regarding the effects of synthetic estrogens on the brain, studies focusing psychiatric disorders in the second and third generation are scarce. The molecular mechanism is of epigenetic type, a hypermethylation occurring at the level of genes affecting mainly the neurodevelopment and the control of the morphogenesis of the sexual organs that represents a significant risk for future generations via a multigenerational effect. This is demonstrated in two striking reports carried out over several generations either at somatic (endometriosis) and psychiatric (psychoses, autism) levels within an informative family. Conversely, the discoveries of evidence of the effects of synthetic progestins on the brain are recent : 2017 in a work which demonstrated in animals (rats exposed in utero) the importance of the role of ER β estrogen receptors (located in the amygdala) in development of autism-like. In humans, for ASD (Autistic Syndrome Disorders) in 2018 and for psychiatric disorders (schizophrenia, depression, bipolarity) in 2019. Artificial estrogens, progestogens, estro-progestogens can trigger the same kinds of psychiatric disorders in children exposed in utero, as well as somatic disorders, prompting them to be banned from women a long time before a pregnancy.

Keywords: Synthetic estrogens, progestins, prenatal exposure, multigenerational transmission

Introduction**Synthetic hormones, a public health problem**

Female sex hormones mainly include estrogens and progestogens. They are usually given to women in the form of synthetic products that mimic the effects of natural hormones, and bind to the same receptors. Since the 1940s, these synthetic hormones have been administered to millions of pregnant women all over the world to "avoid miscarriages" or for comfort, alone or in a cocktail : These include estrogens as diethylstilbestrol (Distilbène® or DES), alone or combined with 17- α -EthinylEstradiol (EE), which is even more potent than DES, and / or Synthetic Progestins (SP) whose impact on the developing brain of children exposed in utero has recently been demonstrated in international studies [1, 2]. In Figure 1 is summarized the chemical degradation of main synthetic estrogens DES and EE in human body and the difference between natural hormone (17- β -Estradiol) and artificial one (17- α -Ethinyl-Estradiol). In France, DES was banned for pregnant women only in 1977, EE in 1980, some SP at various dates while others are still authorized in contraceptives (pills, intra uterine devices, patches), hormone replacement therapy or even prescribed to pregnant women as 17- α -Hydroxyprogesterone caproate, which was withdrawn in France in 2000 and reauthorized in 2011 [2, see Table 34. 3A and B].

Deleterious somatic and brain effects of synthetic estrogens after in utero exposure of children

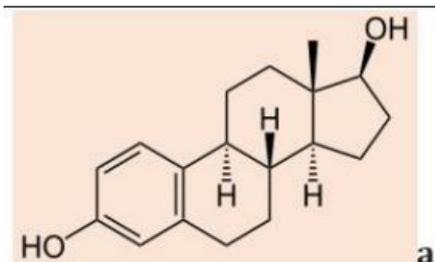
DES was synthesized in 1938 as was EE. However, from 1953 Dieckmann et al. had demonstrated its ineffectiveness on miscarriages [3] but, given its low production cost, it was not patented and manufactured by hundreds of laboratories around the world. It had been banned in the United States for pregnant women in 1971 by the United States Food and Drug Administration, when Herbst and his colleagues discovered that girls exposed in utero presented not only gen-

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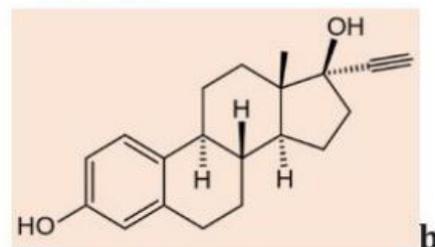
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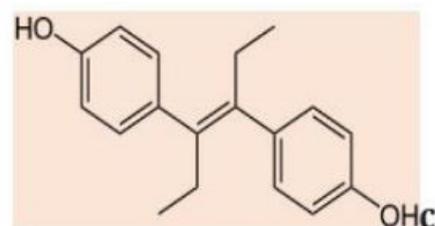
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The natural hormone 17- β -Estradiol (a), non-toxic, is a lipophilic compound that should therefore bind to adipose tissue, but thanks to the detoxifying enzymes Cytochrome P-450 located in the liver, it will be eliminated in the form of a water-soluble product that will be found in the urine in the form of sulfate.



The synthetic hormone 17- α -Ethinyl-Estradiol (EE), toxic (b), often associated with DES in cocktails is also lipophilic. It undergoes other metabolic pathways which lead to the inactivation of Cytochrome P-450, and will remain fixed at the lipid level in young women. Banned in 1980 in Europe for pregnant women, it is however the most marketed hormone in the world because it is used in the composition of the contraceptive pill along with synthetic progesterone.



The toxic Diethylstilbestrol (DES) (c) is a synthetic non-steroidal diphenol with potent estrogenic properties. Very lipophilic, its metabolism in the body is a very harmful degradation, that releases "quinone"-type structures, highly carcinogenic, reactive to proteins and which can bind to DNA. Banned in France for pregnant women since 1977, it is still marketed as an anti-androgen.*

*From Wittliff JL et al, Estrogens IV : Estrogen-like pharmaceutical In : Encyclopedia of Toxicology, Elsevier 2005 (2nd ed.) pp. 254-258.

Figure 1: Degradation of synthetic estrogens in human body.

ital malformations, infertility, but also so-called vaginal cancer with clear cells, specific for this in utero impregnation [4]. The DES-boys were not spared either : they experienced genital malformations (hypospadias, cryptorchidism), increased risk of testicular cancer, sterility or reduced sperm count to the point of total azoospermia. Treated mothers may also have an increased risk of hormone-dependent cancers, especially breast cancer. The links between in utero DES exposure and behavioral disorders are not yet completely recognized while the effects of DES have long been recognized in terms of genital malformations, sterility and cancer, as described by Tournaire et al. [2014] in his "Histoire du Diethylstilbestrol" [5]. Also in 2015 he reported from a national inquiry a significant increase in breast cancer in women exposed to DES compared to those not exposed and to the general population [6]. Nevertheless,

animal studies (rat, mouse) provide convincing data of behavioral disorders from all points of view, whether on DES (7), EE (8), or progestins (9). In humans, few studies have investigated the link between in utero exposure to these synthetic hormones and the onset of severe psychiatric disorders such as schizophrenia, bipolarity, schizo-affective disorders or eating disorders. In the early 1950s, an exploratory

double-blind study was performed at University College Hospital in London on 331 women who received DES early in their pregnancy. Three hundred and nineteen received a placebo, in the same form, and without knowing who was receiving which [10]. Thirty years later, Vessey and his group (1983) started a longterm follow-up of the members of this cohort researching their descendants: they unexpectedly discovered that the girls and boys exposed had twice as many cases of depression and anxiety than in the placebo cohort [11]. It was not until 2010 that the deleterious effects of DES on the nervous system were demonstrated in the USA by O'Reilly and his team in a large epidemiological study on 76,240 American women nurses, known as the "Nurses Health Study"[12]. Among them were 1,612 women exposed in utero to DES. In the latter a statistical increase in depressive and anxiety disorders compared to unexposed girls was identified. In 2012, Kébir and Krebs, psychiatrists of Sainte Anne Hospital in Paris, examining 442 spontaneous testimonies from the HHORAGES patient association noted the presence of psychiatric disorders: 46.7% of mood disorders, 22.9% of psychoses, 6.6% of anxiety disorders, 11% eating disorders and 12.7% others (obsessive-compulsive disorders, violence, addictions) [13]. In 2016, the analysis by Soyer-Gobillard et al. of 1,002

children, 720 of whom were exposed in utero to synthetic estrogens, revealed severe psychotic disorders as well as numerous suicides and attempted suicides that manifested themselves in post adolescence [14]. Lastly, during a national survey conducted by the DES-France Network Association, Verdoux et al, 2017, observed in 2,566 exposed women versus 2,967 unexposed 1.7 times more “DES-Girls” who consulted a psychiatrist, showing that this group is at high risk for mental disorders [15].

Synthetic progestatives too are associated with psychoses and autism of exposed children in utero

Synthetic progestatives were administered to pregnant women alone or as a cocktail with synthetic estrogen, often injected as a progesterone delay. Some of these were forbidden between 1970 and 2000, while others continue to this day to be prescribed [2, see Table 34-1] after the ban on DES and EE for pregnant women. They are also used in the contraceptive pill and intra uterine devices (IUDs). For the latter, we should point out the thousands of complaints for depression filed in 2017 with the French Medicines Safety Agency (ANSM) [16] by women using these IUDs. Three recent studies shed new light on the deleterious effects of in utero exposure to synthetic progestins on neurodevelopment: We conducted observations on a French population (Soyer-Gobillard et al, 2019, 2021) [1, 2] of 1,934 children born from 1200 mothers from the HHORAGES cohort [2, see Table 34. 2A] based on answers to a detailed questionnaire and we observed that most families of this cohort had children exposed to estrogens or to estroprogestins, but only 46 families representing 115 children : among them 62 were exposed to progestins alone and 53 unexposed were used as intra familial controls. We described in the exposed group schizophrenia (25 boys, 4 girls), deep depression, bipolarity (10 girls, 6 boys) [2, and see Figure 34. 2B and Table 34. 3 A and B], demonstrating for the first time the link between prenatal exposure to progestins and psychiatric disorders of children as well as the similarity of these diseases and that of DES/EE exposed children [2, see Figure 34.2 A-D]. In the field of autism, Paul Yao and his group in China, showed in 2017 that prenatal exposure to SP (Levonorgestrel with or without EE) induced autism-like behavior in young rats causing the suppression of ER β (estrogen receptor β) and its target genes that are located in a part of the brain (the amygdala) [9], indicating that ER β expression plays an important role in autism-like behavior development. This was the first demonstration of the potential effect of oral contraceptives on the contribution of autism-like behavior in offspring. In humans the same group (Li et al. 2018) [17] out of 37,863 aged children from 0 to 6 years, found 235 identified cases of ASD versus 682 control subjects. These authors observed that the following factors were present in the mother's history: - use of an SP to prevent a threatened abortion, - use of a progestin contraceptive at the time of conception, - prenatal consumption of seafood or rustaceans contaminated with an estrogen progestogen during the first trimester of pregnancy (100% of mothers), confirming animal results [2, see Table 34.5 A and B].

In a Danish cohort, Baron-Cohen et al. (2018), analyzing physico-chemically the amniotic fluid conserved from 128 ASD male children made the link between children's autism and progestins associated or not with estrogen (EE) ingested by mothers during pregnancy [18].

An epigenetic molecular study proves the link between estrogens in utero exposure and psychoses in children

Recent reports evidenced a link between individual genetic vulnerability and the environment (the administration of artificial hormones, disrupting the endocrine system during pregnancy, constitutes a so-called "environmental" process) in the causes of development of psychiatric illnesses and in those of urogenital malformations. These gene-environment modulations go through so-called “epigenetic” structural modifications of DNA and modify the expression of certain genes involved in neurodevelopment through hormonal disruption. Based on the molecular analysis of peripheral blood from a group of psychotic children (schizophrenic and / or bipolar) from the Hhorages cohort, compared with an intra-family control group and an extra-family control group, Rivollier et al, (2017) were able to show that children exposed in utero to synthetic estrogens (DES, EE) and suffering psychoses exhibited a specific and non-global epigenetic modification (hypermethylation) at the level of two genes involved in neurodevelopment: ZFP57 and ADAM TS9, the latter gene also being involved in control of the morphogenesis of organs, particularly of sexual organs, which are often abnormal after exposure to DES [19].

A time bomb: the multigenerational effect

As early as 2011 with the team of Pr Charles Sultan in Montpellier, we were able to highlight an increase in the prevalence of hypospadias, a malformation of the penis that requires one or more operations, in the grandsons of women treated with DES during their pregnancies [20] indicating a multigenerational effect of this hormone. This was confirmed in 2016 by Tournaire et al. during a national epidemiological survey on DES-daughters initiated in 2013 by the DES-France Network, a survey which also highlights an increase in esophageal malformations, cleft lip or palate, abnormalities of the musculoskeletal and circulatory system in the grandchildren of women prescribed DES [21]. In girls, with Laura Gaspari (2021) we recently reported that DES treatment taken by a mother can impact the endometrium not only in girls exposed in utero but also in her granddaughters of the third generation and likely her grand daughter, demonstrating the multigenerational effect of DES in the development of familial endometriosis [22, see Figure 1]. Regarding psychiatric disorders, the grandchildren of treated mothers in the O'Reilly cohort (2010) [10] were sought out and questioned and Kioumourtzoglou et al. (2018) concluded that out of 47,540 participants spanning 3 generations, DES exposure was associated with neurodevelopmental disorders in grandchildren (cognitive and learning disorders, hyperactivity) demonstrating also its multigenerational effect [23]. More recently (Soyer-Gobillard et al, 2021), we described in an informative family (whose eldest child, used as control was not exposed to DES), the presence of psychiatric disorders in all children exposed in utero of the second generation, together with malformations (endometriosis, hypospadias). We showed also that grandchildren (3rd generation) presented psychiatric disorders as bipolarity or ASD (Asperger syndrome) and that a young grandgrandson was suffering ASD and learning disorder (dyspraxia) while the descendants of the eldest were unharmed [24, see Figure 1 and Table 1]. This also confirms the multi or even trans-generational effect of this endocrine disruptor

In Conclusion: The precautionary principle must be respected for pregnant women

« This is a tragic example of a therapy that looked promising and was based on the best (but faulty) scientific evidence available at the time, which led to the widespread use of a treatment that the physician anticipated would help the patient have a successful pregnancy. However, due to the sensitivity of the developing fetus to an externally administered artificial hormone, unanticipated and severely adverse consequences developed. ... ». This quote from Herbst (2015) [25], the doctor who had banned DES in the USA in 1971 for pregnant women [4], is unfortunately inadequate, because Herbst did not suspect that the product would impact also future generations. All these reported works reinforce the demonstration of the link between synthetic estrogens, progestogens, and / or estrogen-progestogens on the fetal brain and psychiatric disorders development including ASD, associated or not with somatic disorders,

not only in in utero exposed children but also in grandchildren and grand-grandchildren. The epigenetic mechanism of action of these lipophilic chemicals during gestation upon specific genes of the neurodevelopment, implicates de facto a significant risk of multigenerational effect [19-24] that represents a considerable danger for future generations and prompts women to ban all chemicals a long time before a pregnancy.

Authors contributions

M.-O.S.-G.: drafting the manuscript; L.G. and C.S.: revising the manuscript critically for intellectual content.

Competing Interests

The authors declare they have no competitive financial interests; the financing of HHORAGES-France association comes exclusively from the donations of families and of sympathetic individuals.

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