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Neurodevelopmental disorders in children exposed *in utero* to synthetic progestins: Analysis from the national cohort of the Hhorages Association*

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Abstract

The medical and scientific communities have not yet fully acknowledged the undesirable effects of the synthetic hormones that have been administered to pregnant women for decades. The somatic effects of *in utero* exposure to diethylstilbestrol (DES), such as genital malformations, infertility and cancer, have long been recognized but this has not been the case concerning psychiatric disorders. The progestins used in contraception and hormone replacement therapy are known to affect the adult brain, but no data exist on their effects due to *in utero* exposure of children. The Hhorages Association, a national patient support group, has assembled a cohort of 1,200 women who took synthetic hormones during pregnancy. These women had a combined 1,934 children. We obtained full questionnaire responses from 46 women treated with progestins only – and not an oestrogenic cocktail – who gave birth to **115** children. Three groups were observed: Group 1 (n=**18**): firstborn unexposed children, Group 2 (n=**62**): children exposed *in utero* to synthetic progestins, and Group 3 (n=**35**): children born after a previous

pregnancy treated with progestins. No psychiatric disorders were reported in Group 1 and the incidence of psychiatric disorders was drastically elevated in Group 2. Our work shows a striking increase in psychiatric disorders among children exposed *in utero* to progestins and strongly suggests that prenatal exposure is associated with a high risk of psychiatric disorders in adolescence and adulthood, whether accompanied or not by disorders of sex development.

Keywords: Adolescence, adulthood, prenatal progestin exposure, psychiatric disorders.

Introduction

Neuroactive steroids like progesterone play an important role in shaping the CNS structure and function (neurodevelopment, neurogenesis and cognition) throughout the lifespan. Progesterone exerts powerful effects on the brain, such as regulation of neurogenesis and astroglial and synaptic plasticity. Moreover, it regulates the development of neuronal types like Purkinje cells and oligodendrocytes, as well as the myelinisation process. Progesterone exerts a significant influence on the activity of several neurotransmitters involved to the pathophysiology of psychosis, including the dopaminergic, glutamatergic and GABAergic systems. In addition to progesterone itself, it can be converted to dehydroprogesterone and then allopregnanolone (or iso-pregnanolone) (1), potent ligands of the GABA-A receptor. Progesterone elicits its effects by gene transcription, mediated by nuclear progesterone receptors, as well as by non-genomic mechanisms through the activation of a signal transduction pathway. Preclinical studies have provided hints that neurosteroids might be involved in the pathophysiology of psychosis.

Severe psychiatric disorders were recently documented in children exposed *in utero* to synthetic oestrogens like diethylstilbestrol (Distilbene®, DES) and ethinyl oestradiol (EE) (2-4). The actions of these oestrogens involve epigenetic mechanisms (5) and especially differential specific methylations, which were found on the genes ZPF57 and ADAMTS9 in young psychotic patients exposed in utero to DES (6). In this recent work, the authors suggested that in exposed individuals, ZFP57 gene methylation may be associated with psychosis. The ADAMTS9 gene is implicated in the control of organ shape, especially the development and function of the uterus and reproductive organs (7), which are often abnormal after *in utero* DES exposure, as well as in the control of CNS development (8) and several kinds of cancer (9).

Synthetic progestins, widely used for contraception or hormonal replacement therapy, are known to impact the adult brain (10-11), but no data exist on the postnatal effects after *in*

utero exposure. The aim of this work was to determine whether prenatal exposure to synthetic progestins is a risk factor for psychiatric disorders in adolescence or adulthood.

Material and Methods

Our clinical data were collected from 1,200 families (1,934 children) involved in the French Hhorages Association (Halt to Synthetic Hormones for Pregnancies), a patient-support group, using a detailed questionnaire drawn up by practitioners and researchers and described in previous papers (2, 3). We included questions on patient sex, rank among siblings, exposure during gestation, and somatic and psychiatric disorders of the descendants. Most families had children exposed to either oestrogens alone or cocktails of oestrogens and progestins, but only 46 families (115 children) had at least one child exposed to one or more progestins prescribed alone, without oestrogens. In the extensive questionnaires (Registration number to French National Commission of Computer Science and Freedom, CNIL n°1006460), we obtained the family history, including the mother's hormone treatment before and during pregnancy, and the medical records of the children's health problems, including diagnoses, prescriptions and treatments and/or hospitalizations. The psychiatric disorders reported in the questionnaires were classified as: schizophrenia, bipolar disorders (maniac-depressive psychosis), severe depression, behaviour disorders, aggressiveness, and eating disorders. The diagnoses had been made by experienced psychiatrists and the patients received appropriate drugs and psychotherapy with or without hospitalization in specialized institutions. 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.

From the questionnaires completed by the families and returned to the Hhorages Association, it appears that one or several progestins were prescribed and administered to pregnant mothers as shown in the numerous conserved medical prescriptions. The prescribed pharmaceuticals were: 17α-hydroxyprogesterone caproate (synthetic progestin, SP): **32** (Note: withdrawn in 2000 but re-authorized in 2011), 17α-hydroxyprogesterone heptanoate (SP): **10** (Note: withdrawn in 2002), chlormadinone acetate (SP derived from hydroxyprogesterone): **11** (Note: withdrawn on 1970), dydrogesterone (6-dehydroprogesterone, synthetic isomer of progesterone): **4** (Note: against total indication for pregnant women; not withdrawn), "natural progesterone" (derived from soybean, micronized): **4** (Note: not withdrawn), Norethisterone Base (SP): **1** (Note: against total indication for pregnant women; withdrawn in 1998). Total: **62**.

Results

In the entire national Hhorages cohort of 1,934 children, we detected 46 families in which at least one child had been exposed to one or several synthetic progestins.

As shown in **Table 1**, among the 115 children born from these 46 mothers, we observed three well-differentiated groups: Group 1: 18 firstborn unexposed children (9 boys + 9 girls) free of disorders, Group 2: 62 children exposed to synthetic progestins (40 boys + 22 girls), and Group 3: 35 children (21 boys + 14 girls) born after a previous exposure, free of disorders except 1. Group 1 + Group 3 (18 + 35 = 53 children) served as intra-familial controls. Among the 62 children exposed to synthetic progestins (see the list of medications in Material and Methods), 49 presented psychiatric disorders (79.03%), whereas only 6 (4 boys + 2 girls) presented somatic disorders alone (9.67%) and 7 (5 boys + 2 girls) presented no disorder (11.29%).

In Group 2, among the 49 patients affected by psychiatric disorders, 10 suffered from both somatic and psychiatric disorders and 39 from psychiatric disorders alone. Among the psychiatric disorders, we noted: schizophrenia: 29 (**25** boys+ **4** girls); severe depression, bipolar disorder: 16 (**6** boys + **10** girls); and behaviour disorders, aggressiveness, eating disorders: 4 (**0** boys + **4** girls) (**Table 2**). It should be noted that boys mostly suffered from schizophrenic psychosis (**25** boys *versus* **4** girls), whereas girls mostly suffered from bipolar disorder (**10** girls *versus* **6** boys). The questionnaires completed by the families and returned to the Hhorages Association revealed that one or several progestins were prescribed and administered to the pregnant mothers, with the most frequently prescribed drugs being hydroxyprogesterone caproate, heptanoate alone, or heptanoate in a cocktail with other progestins.

In Group 3, among the 35 post-exposed children – that is, born after a previous exposed pregnancy – only one presented a psychiatric disorder as severe depression.

In Group **2,** composed of children exposed to progestins, schizophrenia (n=29), and bipolar disorder and severe depression (n=16) made up most of the psychiatric disorders, whereas eating disorders (n=2) and behaviour disorders (n=2) were less numerous. Seven series of suicide attempts (a series comprising between 2 and 15 suicide attempts per person) were also counted and one death, as shown in **Table 3**, which presents the psychiatric disorders along with their prevalence in the general population (12, 13).

Discussion

Although selection biases (family–patient association) may somewhat affect the impact of our data, the high prevalence of psychiatric disorders in the exposed subjects is quite striking. It should be noted that the intra-familial controls (18 firstborn unexposed *versus* 62 exposed) presented no disease and among the 35 post-exposed (born after a previous treated pregnancy) only one psychiatric disorder was observed. Among the 115 children born from 46 families of the Hhorages cohort, 42 unexposed children had no psychiatric disorders, while of the 62 exposed children, only 7 were without psychiatric disorders (55 with a disorder). As shown in Table 3, our data demonstrate that the prevalence of psychiatric disorders in patients who were exposed *in utero* to progestins was significantly different from the prevalence of the same disorders in the general population: schizophrenia: 29 = 46.77% *versus* 1% in the general population, behaviour disorders: 2 = 3.22% *versus* 3% in the general population, bipolar disorder and severe depression: 16 = 25.80% *versus* 6.3% in the general population, eating disorders: 2 = 3.22% *versus* 1.6%, suicides or suicide attempts: 7 = 11.29% *versus* 0.3% in the general population, and death: 1 = 1.6% *versus* 0.02% in the general population. Seven in utero exposed patients (11.29%) presented no disorder.

We compared our data with the recent results (4) obtained from the Hhorages cohort in which we analysed 1002 patients who were exposed in utero to the synthetic oestrogens diethylstilbestrol and ethinyl oestradiol. Of the 720 patients exposed in utero, 250 boys and 353 girls showed severe psychiatric disorders: schizophrenia, bipolar disorder, severe depression, behaviour disorders, eating disorders, suicide attempt series (612 = 85%) and death (32 = 4.4%). Psychiatric disorders were the same in the groups exposed to oestrogens or progestins, with minor differences: for boys, the number of cases of bipolar disorder seemed less high in patients exposed to progestins than in patients exposed to synthetic oestrogens, with behaviour disorders more prevalent in the latter category. In both categories, schizophrenia was the most prevalent disorder for boys. For girls, however, the proportions of psychiatric cases were nearly the same in the two categories. Bipolar disorder and severe depression were the most abundant disorders in the two categories.

Cumulative evidence from experimental, hormonal, genetic and epidemiological studies suggests a neurodevelopmental origin of most psychiatric disorders. Environmental disturbances are known to increase brain disorder risk, interacting with a genetic predisposition. During foetal life, neuronal differentiation, migration and interaction are managed by molecular processes, regulating the dopaminergic, glutamatergic, and the GABAergic systems. While the

GABA system is the major inhibitory neurotransmitter in postnatal life, GABA-A receptor activation is excitatory during foetal life. In addition to progesterone itself, progesterone is converted to dehydroprogesterone and then to allopregnanolone (or iso-pregnanolone), potent ligands of the GABA-A receptor. These neurosteroids are known to be involved in neuronal and glial development and plasticity, and the regulation of mood and affection. Any neurodevelopmental disruption of this system can induce a dysfunction of cell migration and synaptic integration and may have marked consequences leading to chronic disability.

The data regarding the impact of synthetic progestins on the developing brain are currently conflicting. In adults, progestins have been suggested to exert neuroprotective effects in several animal models of neurological disease (14). After two years of treatment with progestogen via a COC combination (Oral Contraceptive Combination), impaired social behaviour was observed in female rats (15). This combination was also able to alter GABA receptor exposure, increasing the exposure of the gamma2-subunit in the cerebral cortex and thus affecting anxiety behaviour. According to this group, progestin may alter brain function in animal models. In 2016, Willing and Wagner (16) showed that exposure to synthetic progestins during development could impair brain function later in life. These authors noted that many regions of the developing brain are sensitive to progestins, including the mesocortical dopamine pathway, a neural circuit important in rats for complex cognitive behaviour later in life. They found that rats exposed to synthetic progestins during development expressed impaired cognitive flexibility with increased perseveration later in life. Although this data cannot be extrapolated to humans, these authors pointed out the risk of developmental behavioural effects of synthetics progestins prescribed for pregnant women.

Negative mood symptoms have been reported by Andreen et al. (17) in women as a result of progesterone during the luteal phase of the menstrual cycle or progestin in COC. The symptoms are believed to be mediated via the action of allopregnanolone on the GABA-A system. In male patients with early psychosis, Belvederi Murri et al. (18) reported a lower level of progesterone and suggested that this hormone is involved in the pathophysiology of psychotic disorders. This hypothesis is supported by the antipsychotic-like effects observed in animal models of schizophrenia. Recently Slopien et al. (19) reported a reduction in circulating allopregnanolone levels that correlates with depressive symptoms. Conversely, healthy women reported increased anxiety and mood disorders after long-acting subdermal implant of progestogens.

In 2011, Guest et al. (20) reported an elevated concentration of progesterone in a group of 236 first and recent onset of schizophrenia patients and suggested that steroid hormones

influence brain function, underlying schizophrenia and major depressive disorders. Moreover, Buoli et al. (2016) found high DHAS levels in patients with a history of psychotic symptoms, suggesting a role of steroids in the aetiology of psychosis and mood disorders (21).

Lastly, citing the French National Agency of Medicine (22), the independent medical journal "Prescrire", reported that 2,714 adverse effects were signalled in the last year by women using Mirena®, an intrauterine device containing levonorgestrel, a well-known progestin (23). In 85% of the cases, the side effects were mainly related to psychiatric disorders, such as anxiety and depression. [UMO1]

Although a direct relationship cannot be formulated, a link between progestin treatment during foetal life and later psychiatric disorders in offspring should be considered. Since progestins are known to induce GABA receptor activity/neural activation before birth, it is likely that the GABAergic system contributes to schizophrenia, anxiety, depression, panic disorders, epilepsy, autism and other disorders (24). Disruption of GABA signalling in early development alters cell migration and cortical architecture, which then may lead to chronic disability in postnatal life. Our results point out the postnatal consequences of synthetic progestin treatment during foetal life and highlight the potential impact of synthetic progestin. They highlight the need for reevaluation of the potential outcome of progestin administration during gestation.

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Declaration of interest

The authors declare that they have no conflict of interest concerning this work, the Hhorages Association being exclusively financed by memberships and donations.

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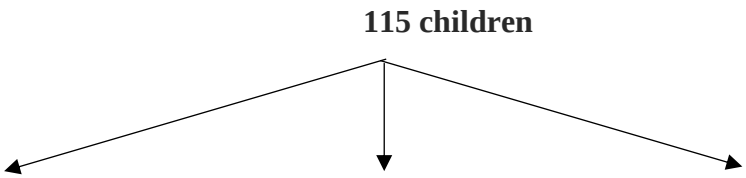
Tables

Table 1. Classification of the three groups of Hhorages children born from 46 families in which at less one child per family has been exposed *in utero* to progestins.



Group 1	**Group 2**	**Group 3**
Firstborn unexposed (n=**18**)	Exposed to synthetic progestins (n=**62**)	Post-exposed n=**35**
	Psychiatric disorders	
0 disorder	n=**49** (79.03%)	n=**1**
	0 disorder n=**7** (11.29%)	
	Somatic disorders only: n=**6** (9.67%)	

Table 2. Total number of psychiatric disorders among the 62 children exposed to progestins.

Schizophrenia (25 boys, 4 girls)	29
Maniac-depressive psychosis (bipolar disorder), severe depression (6 boys, 10 girls)	16
Behaviour disorders, aggressiveness, eating disorders (0 boys, 4 girls)	4
Somatic disorders only (4 boys, 2 girls)	6
With no disorder (5 boys, 2 girls)	7
Total number of exposed children	**62**

Table 3. Prevalence of psychiatric disorders and comparison with the general population.

	Group 1	**Group 2**	**Group 3**	
	Firstborn unexposed **(n=18)**	Progestin exposed **(n=62)**	Post-exposure **(n=35)**	General population
Schizophrenia	(0%)	(n= 29) (46.77%)	(0%)	(1%)
Behavioural disorders	(0%)	(n= 2) (3.22%)	(0%)	(3%)
Bipolar disorder, depression	(0%)	(n= 16) (25.80%)	(n=1) (2.8%)	(6.3%)
Eating disorders	(0%)	(n= 2) (3.22%)	(0%)	(1.6%)
Suicides	(0%)			
Attempts (n=7)	(0%)	(n= 7) (11.29%)	(0%)	(0.3%)
Death (n= 1)	(0%)	(n= 1) (1.6%)	(0%)	(0.02%)
With no disorder		(n=7) (11.29%)		