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Multigenerational Effects of Synthetic Sex Hormones (As Endocrine Disruptor Chemicals) Administered During Pregnancy: A Legal Perspective

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Abstract

Synthetic sex hormones (estrogens and progestogens) were prescribed to pregnant women for decades without regard for the precautionary principle. Data from patient cohorts in the United Kingdom, United States and France indicate a significantly increased rate of somatic malformations and/or psychiatric disorders in children of women who were treated with these hormones during pregnancy. They also highlight the existence of multigenerational effects of exposure to synthetic hormones in several generations: pregnant mothers, their children (prenatal exposure), their grandchildren (via the germinal cells of the exposed fetus) and potentially their great-grandchildren (individuals who were never directly exposed: transgenerational effects).

Data from Danish and Chinese cohorts demonstrated the link between prenatal exposure to estrogens and progestins and autism spectrum disorders. These findings reveal that the damage caused by synthetic sex hormones is delayed. As with all fetal xenoestrogens, the consequences are only visible several years later: psychiatric disorders appear often after the adolescence period and cognitive disorders several years after birth in children and grandchildren. Concerning psychiatric disorders induced by synthetic estrogens and progestogens, legal proceedings were initiated in criminal court by families belonging to the French patient association HHORAGES-France from 2001 to 2017 and following their failure, in civil court from 2018 to 2024. This last procedure failed due to the ten-year limitation period for complaints before a civil court. This article describes these actions, their outcomes and the reasons for their failure, and also the current efforts to amend the law through parliamentary action, in connection with recent scientific advances.

Keywords: Endocrine Disruptors, Synthetic Hormones, Somatic and Psychiatric Disorders, Criminal Court, Civil Court

Introduction

Synthetic sex hormones, such as the estrogens diethylstilbestrol (DES) and ethinyl estradiol (EE) and the progestogens often prescribed in a slow-release form (e.g. Progesterone Retard Pharon, 17- α -hydroxyprogesterone caproate, by

weekly injection), are endocrine disruptors that were administered to pregnant women for decades without undergoing rigorous safety studies before their market release. The concept of endocrine disruptor is based on the combination of four parameters:

- Epidemiological data,
- Experimental data from animal studies,
- Observations of wildlife, and
- Analysis of their deleterious effects in humans and animals.

Already shortly after DES synthesis by Dodds et al. in 1938, Lacassagne demonstrated that this petroleum-derived substance, which possesses potent estrogenic activity, is carcinogenic and acts as a tumor promoter in mice [1,2]. Furthermore, in 1954, Dickman et al showed that DES is as effective as a placebo [3]. These findings were disregarded because the product was inexpensive to manufacture, unpatented, and therefore, highly lucrative. Consequently, it was administered to many pregnant women worldwide. Current estimates indicate that more than 50 million people have been directly or not prenatally exposed to DES. This hormone was ultimately banned for pregnant women in the United States of America (USA) in 1971 (in 1977 in France and 1982 in Hungary) following the discovery by Herbst et al. of clear-cell vagina adenocarcinoma in girls who had been prenatally exposed to DES [4,5]. Currently, through the analysis of its medium- and long-term pathological consequences, DES is at the origin of the concept of the Fetal Origins of Adult Disease (FOAD) hypothesis.

17- α -Ethinylestradiol (EE), often administered in combination with DES, was banned for pregnant or breastfeeding women by the European Community in 1980 (as it can cause endometrial cancer and/or thromboembolic disorders), but it is still used in combination with synthetic progestins in contraceptive pills. Consequently, for pregnant women, the only remaining options for prescribers were synthetic progestins, such as 17- α -hydroxyprogesterone caproate and other progestogens. 17- α -hydroxyprogesterone caproate has a remarkable history: it was withdrawn in 2000 for pregnant women and reauthorized in 2011, and was banned again in the USA in 2022 and in France in 2024 following the discovery by Murphy et al. of pediatric cancers in the offspring of women treated with this drug during pregnancy [6]. In summary, DES has been banned for pregnant women since 1971 (USA) and 1977 (France), but its effects are still observed in the subsequent generations. Synthetic hormones (DES, EE, synthetic progestins) were often prescribed in cocktail not only to women who had a miscarriage or were at risk of miscarriage, but also to improve pregnancy comfort or even as a “morning after pill”.

The effects of these synthetic sex hormones in the second and third generations (G2 and G3) of descendants of pregnant women treated with these drugs (first generation; G1) include somatic conditions (e.g. malformations of the male and female reproductive systems, infertility and cancers), musculoskeletal anomalies (hemimelia, agenesis, craniosynostosis), neurodevelopmental disorders, severe depression, bipolar disorder, schizophrenia, eating disorders, autism spectrum disorders (ASD) and cognitive problems [7-17]. Moreover, gender identity and sexual orientation disorders have been reported in individuals exposed to DES *in utero* (G2) [18,19].

Only in 2017, the molecular link between *in utero* exposure to DES and other estrogens and psychotic disorders was demonstrated by F. Rivollier et al. [20]. An epigenetic mechanism was identified using peripheral blood samples from G2 individuals with psychotic disorders and their intrafamilial control (an unexposed older sibling): DNA hypermethylation (the addition of a methyl group CH₃ at a specific location) of two genes involved in neurodevelopment. This also might explain the observation of multigenerational effects: in the pregnant woman (G1), the prenatally exposed child (G2) and grandchild(ren) (G3; due to the prenatal exposure of reproductive germ cells in the G2 fetus) and possibly G4 [21]. In the same year, the mechanism of action of progestins on the brain was deciphered by P. Yao's team in China [22]. They showed in rats that after *in utero* exposure to progestins, the ER β receptors for estrogens (and progestogens) located in the amygdala (a brain region) are downregulated, inducing ASD-type disorders.

Methodology

Data came from the HHORAGES-France retrospective cohort that includes 1,200 women who were treated with DES and other synthetic estrogens (e.g. EE) and/or progestogens/progestins (e.g. 17- α -hydroxyprogesterone caproate) (G1) and their children (~2,000; G2) exposed or not *in utero* to these drugs. Families completed a very detailed medical questionnaire described in a chapter of the book “State of the Art of Therapeutic Endocrinology” entitled: “Behavioral and somatic disorders in children exposed *in utero* to synthetic hormones: A testimony-case study in a French family troop” [23]. The Montpellier University Hospital ethics committee approved the present study on April 20, 2026 (ID IRB No 202601532), and all patients gave their informed consent through the HHORAGES France Association. The questionnaire and the collected data used to study the psychological and somatic effects of the synthetic hormones administered during pregnancy were approved by the French National Commission for Information Technology and Liberties (CNIL) (J B/EM/DC042793, N° 1006460).

Findings and Discussion

Hhorages-France Cohort

The HHORAGES-France retrospective cohort included 1,200 women who were treated with synthetic sex hormones during at least one of their pregnancies and 1,934 G2 individuals. Among the G2 individuals, 302 were unexposed (first

born children: 154 girls and 148 boys), 1,225 were prenatally exposed to synthetic hormones (735 girls and 490 boys); n=1,163 exposed to estrogens and/or progestins, among whom 395 only to DES (142 girls and 253 boys), and 62 only to progestins (22 girls and 40 boys); and 407 were post-exposed (i.e. born after a previous pregnancy during which the mother received synthetic sex hormones; 240 girls and 167 boys). The unexposed first-born children did not report any somatic/psychiatric disorder and served as intra-familial control. Table 1 presents three examples of the prescribed synthetic sex hormone regimens.

A number of families compiled case files, gathered by a law firm specialized in public health, that were suitable for presentation in court. The main challenge was preserving evidence over a period of more than fifty years, particularly medical prescriptions, medical records and personal health booklets. Nevertheless, several cases were presented before the Paris Criminal Court starting from 2002.

Treatments of Mrs. A Medical history: one miscarriage at 6 weeks of amenorrhea 2 years before the prescription of synthetic sex hormones. Normal hysterosalpingography. Deficient hormone levels (which are now known to be due to the previous miscarriage [24]). First Pregnancy (1966-67): At week 7 of amenorrhea: EE 100 µg/day (19 µg/kg/day). From week 10 to week 20: DES (Distilbene® 15 mg/day; 288 µg/kg/day) + EE 100 µg/day. From week 20 to week 37: DES (Distilbene® 15 mg/day) + EE 250 µg/day (48 µg/kg/day) + 17-alpha-hydroxyprogesterone caproate (Progesterone Retard Pharon 500 mg/week; 9.6 mg/kg/week). A baby girl was born at term; Apgar score 10/10. No problems during pregnancy and childhood. However, 28 years later, she committed suicide after living with bipolar and eating disorders for 10 years and 14 suicide attempts. Psychiatric disorders began after adolescence (18 years of age). In addition, infertility was diagnosed. Second Pregnancy (1971): At week 6 of amenorrhea: EE 250 µg/day. From week 8 to week 37: EE 500 µg/day + DES (Distilbene® 25 mg/day) + 17-alpha-hydroxyprogesterone caproate (Progesterone Retard Pharon, 500 mg/day). A baby boy was born at term; Apgar score 10/10. No problems during pregnancy and childhood. However, 27 years later, he committed suicide after 10 years of schizoaffective disorder that started at the age of 18 years (no previous history of suicide attempts). Treatments of Mrs. B† Medical history: one miscarriage at week 6 of amenorrhea 2 years earlier. Treatment during pregnancy (1962-63) was identical to that of Mrs. A, following the protocol defined by the gynecologist and administered between months 3 and 6 of pregnancy. A boy was born with hydatid testicular torsion. Psychiatric disorders and delirium began at 19 years of age without suicide attempts and schizophrenia was diagnosed. At the age of 39 years (2002), he committed suicide. Treatments of Mrs. C Medical history: infertility, normal hystero-graphy. Treatment during pregnancy (1968-69): DES (Distilbene® 25 mg) + 17-alpha-hydroxyprogesterone caproate (Progesterone Retard Pharon 250 mg/day, one injection every 7 days) for 2 months, from December 26, 1968, to February 23, 1969. A baby boy was born at term with unilateral cryptorchidism (surgically corrected at the age of 12 years) and childhood characterized by retreating into sleep. He experienced behavioral difficulties during adolescence and schizophrenia was diagnosed at the age of 32 years (2001), treated with neuroleptics. He died of cardiac arrest at the age of 47 years (2016); the autopsy revealed that one ventricle was larger than the other, suggesting a cardiac effect of the neuroleptics [25].

Table 1: Hormonal Treatments Administered to Three Women During Pregnancy, from the HHORAGES Cohort. HHORAGES-France Data

A Preliminary Investigation and Three Formal Complaints Following the Interruption of the Statute of Limitations

Before filing a criminal party complaint, on February 10, 2001, Mrs. A (Table 1) lodged a standard complaint against the laboratories UCEPHA and ROUSSEL, which marketed Distilbene® and EE, respectively, when they were prescribed, to the plaintiff, alleging the administration of “harmful substances” and “involuntary homicide.” A preliminary investigation was conducted before being consolidated with the formal judicial investigation. The complaint filed by Mrs. A tolled the statute of limitations because Mrs. A’s second child committed suicide on February 14, 1998 (less than three years before), thus pausing the statute of limitations. On May 28, 2002, the representative of the GERBA Laboratory, which has the marketing authorization for Distilbene® since March 6, 2001, explained that the product was still marketed

for the treatment of prostate cancer, but had been strictly contraindicated for pregnant women since 1977 due to the teratogenic (genital malformations) and carcinogenic risks posed to children exposed in utero [5].

During May and July 2003, representatives from the French Association for Aid to Victims of Medical Accidents (AAVAM), National Union of Friends and Families of the Mentally Ill (UNAFAM) and HHORAGES-France (Stop Artificial Hormones in Pregnancies) were interviewed and provided several lists of individuals who had given testimony and consented to speak with police investigators, as "likely to have suffered harm due to the administration of Distilbene®". The HHORAGES association had received, as of July 2003, 340 files describing 400 cases of psychiatric disorders and estimated that the causal link to synthetic hormones, specifically Distilbene® and EE, was 89% certain. Several of the interviewed witnesses described the psychiatric disorders affecting their children and hypothesized a link between these disorders in their children and their own intake of synthetic sex hormones during pregnancy. They explained that they had become aware of a potential connection following the publication of scientific studies around the year 2000 [26]. Although none of the interviewed mothers filed a formal complaint, they unequivocally expressed the desire that the potential link between the synthetic estrogens administered by doctors during their pregnancies and the psychiatric disorders developed by their children should be investigated. An analysis of the initial complaint, prepared at the request of the Public Prosecutor's Office by the medical expert Dr. B., was added to the case file. However, after reviewing the current state of knowledge on the subject, Dr. B. concluded that the epidemiological studies conducted to date on "DES children" (G2) did not validate this hypothesis because they all contained numerous biases that precluded any definitive conclusion. Therefore, complaints on DES psychiatric effects appeared premature based on the scientific knowledge on the subject at that time.

Filing of Complaints with the Criminal Court

On August 9, 2005, Mrs. A filed a formal complaint with the senior investigating judge at the Paris Regional Court (France) alleging involuntary homicide, involuntary bodily harm, the intentional administration of harmful substances, and fraud. She stated that her two children, born in 1967 and 1971, had both been exposed to synthetic sex hormones in utero. Specifically, to prevent miscarriage, her doctor prescribed Distilbene® and EE during both pregnancies. She thought that these products had caused severe psychiatric disorders in her children, notably recurrent depression and schizophrenia, leading both of them to commit suicide. Her daughter, born on March 2, 1967, took her own life on August 29, 1995, and her son, born on September 10, 1971, ended his life on February 14, 1998. The existing studies allowed the Public Prosecutor's Office to assert that a scientific challenge existed, and therefore a causal link could not be ruled out a priori, although proving such a link scientifically appeared extremely difficult.

As the case of Mrs. B was similar to that of Mrs. A (same hormonal treatment during pregnancy and schizophrenia, next suicide of the son exposed in utero to synthetic sex hormones) (Table 1), in the interests of the proper administration of justice, the two cases were consolidated into a single prosecution.

In late 2012, Mrs. A. and Mrs. B., accompanied by their criminal defense lawyer, were questioned by the Investigating Judge at the Public Health Division, who listened to them with great respect. This judge was a specialist in major public health scandals in France, including asbestos, contaminated blood, Creutzfeldt-Jakob disease, and Chernobyl cloud, and a coordinator of the French Public Health Division since 1981. Sometime later, she decided to place the three laboratories manufacturing Distilbene®, EE and Progesterone Retard Pharon under formal investigation. However, on March 13, 2013, her tenure as a judge at the Public Health Division was brought to an end before she could formally place the laboratories under investigation.

The path taken by the third family (Mrs. C, Table 1) was even more complex: after filing a formal complaint involving a civil party claim, the Public Prosecutor recommended refusing to open a judicial investigation on the grounds that the statute of limitations had expired for both the offense of fraud and the offense of causing unintentional bodily harm. This was because more than three years had elapsed since the harmful event came to light, dating back to the child's adolescence or, at the latest, to the publication of the study by Dr. Verdoux et al. in 2000, which suggested a causal link between synthetic sex hormones and psychiatric conditions in children exposed in utero [26]. Following an appeal to the Court of Cassation, a rejection by the court, and a subsequent appeal, the complaint was finally accepted and consolidated with the earlier ones. On January 25, 2013, case file of Mr & Mrs. C and family was joined to the ongoing proceedings.

In addition, the complaints of two other couples (Mr. & Mrs. D and Mr. & Mrs. E) were added to these three complaints. Mrs. D was prescribed the same drug regimens described in Table 1 and the boy exposed in utero received a diagnosis of schizophrenia. Mr. and Mrs. D filed a complaint with a civil party claim on November 27, 2007, alleging unintentional bodily harm and fraud. The investigating judge issued an order on July 25, 2008, ruling (contrary to the Prosecutor's recommendations) that there were grounds to open an investigation. The judge reasoned that the statute of limitations had been interrupted due to the connection between this complaint and other complaints investigated by the same office. The complaint filed by the couple was joined to the initial proceedings.

Mrs. E was treated with Distilbene® during pregnancy and the prenatally exposed daughter had serious depressive

disorder and ovarian cancer. However, the case of Mr. and Mrs. E was considered inadmissible on December 19, 2014, in accordance with the Public Prosecutor's submissions, on the grounds that based on the evidence submitted, the statute of limitations had expired for the alleged offenses of administering harmful substances and causing unintentional harm to the physical integrity of others linked to psychiatric disorders. Regarding the new allegations of unintentional injury linked to the development of ovarian cancer, the judges noted that these matters were not included in the initial referral and that the Public Prosecutor had not issued a supplementary indictment. In a ruling dated June 10, 2015, the Investigating Chamber, hearing an appeal filed by the family, upheld the inadmissibility order of December 19, 2014.

The patient association HHORAGES-France also joined the proceedings as a civil party on November 16, 2010, but its claim was quickly declared inadmissible on the grounds that the association could not demonstrate any personal harm directly linked to the offenses of homicide, unintentional injury and fraud.

Following expert assessments by two specialists (an endocrinologist and a psychiatrist), whose conclusions were judged inconclusive, the Court issued a dismissal order on November 17, 2015. For this, it relied on the negative findings by Verdoux et al. (2007) on a causal link between psychiatric disorders in prenatally exposed children and the administration of synthetic estrogens to mothers during pregnancy, rather than on the positive findings by O'Reilly et al. (2010) [11,27]. This large epidemiological study on 76,240 American female nurses ("Nurses' Health Study") suggested that prenatal exposure to DES increases the risk of heavy depression in adult life.

The four families (A, B, C, D) appealed the decision based on the results of a 2016 study by Soyer-Gobillard et al. in which they analyzed data on 1,002 children from the retrospective HHORAGES-France cohort, among whom 720 were exposed in utero to synthetic estrogens. In DES children (G2), but not in their non-exposed older siblings, they found severe psychotic disorders in post-adolescence that led to numerous suicide attempts and suicides. Moreover, a 2017 article in PLOS ONE by Rivollier et al. demonstrated DNA hypermethylation of two genes involved in neurodevelopment in DES children with psychosis versus their intrafamilial non-exposed control [12,20]. Despite these new findings, the results of the Verdoux study (2007) prevailed, and the Court ruled against the plaintiffs once again on November 9, 2018, bringing a criminal proceeding spanning over 17 years to a close due to "lack of evidence." A few months later, a new article by Verdoux et al. (2017), contradicted the own previous 2007 publication, but ten years too late! In this national survey on DES daughters, Verdoux et al. found that DES daughters (n=2,566) were 1.7 times more likely to have consulted a psychiatrist compared with controls (n=2,967 unexposed women), showing that this group is at higher risk of mental health disorders [27,28].

Filing of Complaints with the Civil Court

The families had no choice but to turn to civil proceedings. Two groups were formed: families A, B, and C who remained together, and family D who was joined by a mother (Mrs. E), her DES daughter (Mrs. F) and their family. The analysis of the procedures and their results are presented chronologically.

Mrs. E & Mrs. F & Family

Mrs. F realized that she was a DES daughter in 1992 when a uterine malformation and a small cervix, characteristic of DES exposure, were noted and subsequently experienced bed rest throughout her 1997 pregnancy and a Caesarean delivery. She developed adhesions following this Caesarean section, conditions associated with estrogen exposure, which necessitated many interventions (hysterectomy in 2008 for endometriosis, oophorectomy in 2010), as well as an autoimmune disease (myelodysplastic syndrome with peripheral thrombocytopenia of the purpuric type), inability to have more children, and inguinal hernia. Mrs. F also reported eating disorders, depression, alcoholism, psychiatric hospitalizations and suicide attempts.

After filing a complaint on January 5, 2018, against UCB Pharma, the manufacturer of Distilbene® (a company based in Belgium), Mrs. E, Mrs. F and their family received an unfavorable ruling from the civil court. In a judgment dated January 23, 2020, the court rejected the plea of inadmissibility based on the statute of limitations raised by UCB Pharma, and dismissed all claims made by Mrs. E, Mrs. F and their family and ordered them to pay all legal costs. Ms. E, Ms. F, and their family lodged an appeal against this judgment on February 6, 2020. Unfortunately, following an expert opinion submitted by UCB Pharma that considered the results by Rivollier et al (Appellants' Exhibit No. 23) unconvincing and highlighted the need of more research, the judges concluded that conclusive evidence was lacking [20]. UCB Pharma submitted the 2007 study by Verdoux that indicated no evidence of a link between prenatal DES exposure and the onset of psychiatric symptoms, but not the 2017 article that contradicted their previous one [27,28]. The appeal was dismissed on October 7, 2021, and the matter came to an end for this family.

Mr. & Mrs. D.

On October 4, 2017, Mr. and Mrs. D and their son, assisted by his court-appointed guardian, filed a lawsuit against UCB Pharma before the Nanterre Tribunal de Grande Instance (Regional High Court). The Primary Health Insurance Fund (CPAM) of Nice was also present as a party. They sought to establish liability and obtain compensation for damages attributed to the son's in utero exposure to Distilbene®. In a judgment dated September 19, 2019, the Nanterre high court ruled that the claims of Mr. and Mrs. D and their son were inadmissible on the grounds that the statute of

limitations had expired.

Then, Mr. and Mrs. D decided to appeal the decision to the Versailles Court of Appeal. In a ruling dated April 15, 2021, served on May 4, 2021, the Court of Appeal upheld the lower court's judgment in its entirety.

Therefore, Mr. and Mrs. D lodged an appeal with the Court of Cassation. On March 30, 2023, having determined, following an analysis of the evidences debated by the parties and exercising its sovereign power to assess the date of medical stabilization, that said date should be set in 2005, the Court of Appeal correctly concluded that the claims were time-barred. This conclusion was based on the former Article 2270-1 of the French Civil Code that fixed a ten-year limitation period, subsequently reduced to five years upon the entry into force of Law No. 2008-561 of June 17, 2008, pursuant to Article 2224 of the Civil Code. On these grounds, the Court dismissed the appeal and ordered Mr. and Mrs. D and their son to pay the costs. Pursuant to Article 700 of the Code of Civil Procedure, it rejected the claims.

Mr. and Mrs. D decided to lodge a complaint with the European Court of Human Rights. The European Court of Human Rights, sitting on February 8, 2024, as a single-judge formation in accordance with Articles 24 § 2 and 27 of the Convention, examined the aforementioned application as submitted. The application was based on Article 2 § 1, Article 6 § 1, and Article 13 of the Convention. On the basis of all the material in its possession, and insofar as the matters complained fell within its competence, the Court found that they did not disclose any appearance of a violation of the rights and freedoms guaranteed by the Convention or its Protocols and that the admissibility criteria set out in Articles 34 and 35 of the Convention were not met. The Court declared the application inadmissible.

Mrs. A, Mrs. B† (Mrs. B having passed away [17-09-2023], her claim was extinguished), and Mrs. C: On July 25, 2024, the judgment delivered by the Civil Division of the Nanterre Judicial Court on the two consolidated cases also was unfavorable. The plaintiffs and their families had filed suit against S.A. UCB PHARMA (manufacturer of Distilbene®), S.A. EFFIK (manufacturer of EE), and S.A. BAYER HEALTHCARE (manufacturer of synthetic progesterone). The Court declared all claims brought by the plaintiff families A and C inadmissible due to the statute of limitations without even having taken into account their lawyer's arguments on the merits of the case. Furthermore, pursuant to Article 700 of the Code of Civil Procedure, Mrs. A and C were ordered to "compensate" UCB PHARMA and EFFIK by paying them a specified sum.

Scientific Knowledge when the Complaints were Filed

In the period 2001-2016, two cohort studies on DES by Vessey et al (1983) in the United Kingdom and by O'Reilly et al (2010) in the United States had been published. In the early 1950s, an exploratory double-blind study was started at University College Hospital in London on 331 women who received DES at the beginning of pregnancy and on 319 women who received a placebo [11,28,30]. Thirty years later, in 1983, Vessey and colleagues analyzed the outcomes of these women and their descendants. They discovered that the prevalence of depression and anxiety was twice as high in DES children (G2) than in the placebo group. In 2010, DES deleterious effects on the nervous system were confirmed in the USA by O'Reilly and colleagues in a large epidemiological study on 76,240 American female nurses, known as the "Nurses' Health Study" [11,29].

Regarding EE, the only existing studies were in animals, specifically rats, showing behavioral alterations in pups exposed to EE in utero; these studies were disregarded by the judges ("Animals aren't humans!" they said) [31,32].

Recent Studies (2015–2025)

Advances in Cellular and Molecular Biology

In 2017, P. Yao's team found that prenatal exposure to levonorgestrel (a synthetic progestin) could induce ASD-like behaviors in rat pups exposed in utero. An analysis involving ultrafine cytology, biochemistry, and molecular biology of the brains of rats exposed to this progestin showed that progesterone and estrogen (ERβ) gene receptors are localized in the amygdala (a brain region) and their expression is altered (downregulation via DNA hypermethylation of the ERβ gene promoter) following treatment of the dams during pregnancy. This work was extensively corroborated and expanded by the same team in 2018 through a large-scale case-control epidemiological study in Hainan Island (population 8 millions) [15,22]. The study covered 37,863 children aged 0 to 6 years and identified 235 children with ASD and 682 matched controls. Comparison of candidate factors in the cases and controls showed that ASD prevalence in children was associated with the use of progestin to prevent abortion (15.3% of mothers), use of progestin contraceptives at conception time (11% of mothers), and consumption of progestin-contaminated seafood in the first trimester of pregnancy (all mothers). To confirm these findings, they fed zebrafish treated with synthetic progestin (norethindrone) to pregnant rats and found that their offspring displayed autism-like behavior. The authors suggested that prenatal progestin exposure may be associated with ASD development.

Liquid Chromatography and Mass Spectrometry Studies

In 2015, Baron-Cohen et al. analyzed by liquid chromatography and mass spectrometry amniotic fluid samples (previously frozen) from 128 boys with ASD from a Danish Historic Birth Cohort. They found that the fetal concentrations of sex hormones (especially progesterone and 17- α-hydroxyprogesterone) were higher in children with ASD compared with

matched controls. This was the first evidence that fetal steroidogenic activity is increased in autism. Moreover, using the same cohort and methods, the authors showed the prenatal estrogen and progesterone concentrations were higher in the amniotic fluid of boys who developed autism (n=98) compared with boys without autism (n=177) [33,34]. They concluded that prenatal sex hormone concentration alterations influence brain development and sexual differentiation and also contribute to the risk of autism.

The scientific Revolution of Epigenetics

As demonstrated by Skinner et al., at the origin of all this epigenetic work, deleterious epigenetic effects are transmitted to the subsequent generations (multi- and trans-generational effects) via the fetal germ cells exposed in utero [21,35]. Three epigenetic mechanisms are possible: DNA methylation (hyper- or hypomethylation), histone protein modification, and microRNA expression alteration [36].

Patients from the HHORAGES-France cohort were used to study the molecular basis of the association between prenatal exposure to synthetic estrogens (DES-EE) and psychotic disorders (e.g. schizophrenia and bipolar disorders) [20]. Blood samples from 69 siblings (n=37 prenatally 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 of 411,947 CpG (cytosine near guanine) sites/genome. Peripheral blood samples were used because it was previously reported that the methylation profiles in brain and blood samples are rather similar. This analysis showed that DNA methylation at the ADAMTS9 gene was different between exposed and unexposed individuals. Moreover, differential DNA methylation of the ZFP57 gene was observed in exposed individuals with psychosis compared with exposed individuals without psychosis. The authors suggested that in exposed individuals, psychosis is associated with specific methylome modifications that affect gene activity and consequently might alter neurodevelopment and neuroplasticity.

Cohort Studies

In 2018, Kioumourtoglou et al. using data from the Nurses'Health Study II cohort (47,540 women spanning three generations) [17], found attention-deficit/hyperactivity (ADHD) in G3 children (i.e. the grandchildren of the women who took DES during pregnancy). ADHD etiology involves a combination of genetic and environmental risk factors. The authors concluded that "DES exposure is associated with multigenerational neurodevelopmental disorders".

In 2016 and in 2019, using data from the retrospective HHORAGES-France cohort, Soyer-Gobillard and colleagues described the presence of severe psychiatric disorders in children (G2) who were in utero exposed to synthetic sex hormones. Although experts commissioned by the three different companies that manufacture these synthetic hormones questioned the validity of this "biased" cohort, the association is beyond doubt. Furthermore, a link between DES and autism was identified in an "informative" family where the eldest child was not prenatally exposed [12,13,16].

Lastly, in a French national survey, Verdoux et al. in 2017 found that DES daughters (G2) (n=2,566) were 1.7 times more likely to have consulted a psychiatrist compared with controls (n=2,967 unexposed women), showing that this group is at higher risk of mental health disorders [28].

How Could Victims Gain Recognition and Compensation Despite the Statute of Limitations?

In French law, the statute of limitations is a general legal principle that defines the timeframe beyond which a civil or criminal legal action is no longer admissible [37]. Consequently, it serves as a legal mechanism for the acquisition or extinguishment of rights based simply on their possession over a specific period. It can apply to real or personal rights, concerning movable or immovable property. However, the majority of European systems have adopted the opposite approach, prioritizing the protection of victims who initiate criminal proceedings [37]. In Spain, Belgium and Italy, criminal proceedings, even those concluding with a dismissal or a decision not to prosecute, can interrupt, suspend, or defer the civil statute of limitations, or at the very least influence its deadline. In the USA, the situation varies by state, but in many instances, the dismissal of criminal charges has no impact on the course of civil litigation. Therefore, the current French approach appears isolated, excessively formalistic, and difficult to reconcile with the fundamental right of access to the courts.

Conclusion

Current data demonstrate that some hormonal substances, when administered in utero, produce deleterious effects that are delayed in onset and sometimes transmissible to the subsequent generations. Maintaining a rigid statute of limitations in this context effectively ensures the *de facto* civil immunity of the involved economic actors. Starting in 2001, following the suicide in February 1998 of Mrs. A's second child that interrupted the statute of limitations, three mothers and their families filed criminal complaints. They were subsequently joined by several other plaintiffs. Collectively, these plaintiffs first faced charge dismissal due to lack of evidence (Court of Cassation and also European Court of Justice). After a battle spanning more than 24 years, the victims were denied any compensation and, above all, any recognition of their status as victims, simply because they had placed their trust in the French criminal and civil justice systems. They endured a human tragedy (their children's bad health and suicide) (Table 1), an extremely lengthy criminal proceeding with dismissal of charges, and subsequently rejection of their civil claims due to the statute of limitations.

In conclusion, this represents a two-fold denial of justice: criminal (lack of recognition as victims) and civil (impossibility of even arguing the merits of the case). Following the initial victims' setbacks, the only option to ensure that the fight can continue for all the other victims is to draft a new bill for the French Chamber of Deputies for abolishing the ten-year statute of limitations. This new bill will be presented to the deputies of the National Assembly in few months. The aim of the proposed reform is to guarantee the effective right to compensation by eliminating the civil statute of limitations for damages linked to prenatal exposure to substances recognized as harmful to human development. From a political and legal standpoint, this initiative aligns with a fundamental demand for social and health justice. It draws lessons from half a century of medical disasters, foremost the DES scandal that exposed the structural limitations of standard statutes of limitations when dealing with injuries that manifest late, sometimes across generations. The current system leads to a situation that is legally and humanly untenable: victims, who have acted diligently, initiating criminal proceedings and cooperating over many years, find that any civil recourse is denied to them simply because the proceedings lasted more than a decade. This situation constitutes a clear infringement of the right of access to the courts, the principle of full reparation for damages, and the citizens' legitimate trust in the judicial system. The law can no longer ignore the lessons of science.

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Conflicts of Interest: MOS-G is a researcher and President (unpaid) of the HHORAGES-France Association and a mother concerned with DES and other synthetic hormones. The 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. HHORAGES France Association is financed exclusively by subscriptions and donations.

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