World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Research Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 7
Page: 495-511

MUSCULOSKELETAL ANOMALIES IN THE SECOND AND THIRD GENERATIONS OF CHILDREN AFTER IN UTERO EXPOSURE TO XENOHORMONES AS ENDOCRINE DISRUPTOR CHEMICALS

Marie-Odile Soyer-Gobillard*[1,2], Laura Gaspari-Sultan[3,4], Charles Sultan[3,4]

[1]Sorbonne University, CNRS, 75016 Paris, France.

[2]Association HHORAGES-France, 66100 Perpignan, France.

[3]Unité d'Endocrinologie-Gynécologie Pédiatrique, CHU Montpellier, University Montpellier, 34090 Montpellier, France.

[4]CHU Montpellier, University Montpellier, Centre de Référence Maladies Rares du Développement Génital, Constitutif Sud, Hôpital Lapeyronie, 34295 Montpellier, France.

Article Received: 24 May 2026 | | ***Article Revised: 14 June 2026*** | | ***Article Accepted: 05 July 2026***

***Corresponding Author: Marie-Odile Soyer-Gobillard**
Marie-Odile Soyer-Gobillard.
DOI: https://doi.org/10.5281/zenodo.21371086

How to cite this Article: Marie-Odile Soyer-Gobillard, Laura Gaspari-Sultan Charles Sultan (2026) MUSCULOSKELETAL ANOMALIES IN THE SECOND AND THIRD GENERATIONS OF CHILDREN AFTER IN UTERO EXPOSURE TO XENOHORMONES AS ENDOCRINE DISRUPTOR CHEMICALS. World Journal of Pharmaceutical Science and Research, 5(7), 495-511.

ABSTRACT

Diethylstilbestrol (DES) and ethinyl estradiol (EE), xenohormones with potent estrogenic properties, were synthesized in 1938; their use in pregnant women was subsequently banned between 1971 and 1982 for the former and in 1980 for the latter. In addition, progestins (delay or not) were frequently used with DES and/or EE and have since served as replacement compounds. In the present work, based on data from a retrospective French cohort of patients whose mothers (first generation) were treated with DES, EE and/or synthetic progestins during pregnancy, we highlight the presence of congenital malformations, particularly of the musculoskeletal system, in second (directly exposed *in utero*) and third-generation girls and boys. The analyzed data were from 17 families and included 30 second-generation children (20 girls and 10 boys who were prenatally exposed) and 31 third-generation grandchildren (7 girls and 24 boys). Some of the mothers (second generation) of third-generation grandchildren received hormonal treatment (progestins) to promote fertility or for *in vitro* fertilization procedures. The mechanisms involved in the teratogenic effects of these endocrine disruptors are discussed. As the descendants of women treated with DES represent more than 50 million people worldwide, the exposure to exogen sex hormones and other widespread endocrine disruptor chemicals might negatively affect the life of hundreds of millions of people worldwide.

KEYWORDS: Diethylstilbestrol, synthetic estrogens, progestins, endocrine disruptors, anatomical malformations.

1. INTRODUCTION

After the synthesis of diethylstilbestrol (DES) in 1938 by Dodds et al.[1] and despite the initial work by Lacassagne,[2] in the same year, who showed its carcinogenic effects in mice, this petroleum derivative with powerful estrogenic effects was marketed worldwide and manufactured by hundreds of pharmaceutical laboratories. Already in 1954, Dickmann et al.[3] showed that it was not more effective than a placebo. However, DES was banned in the USA only in 1971 (and in France in 1977) following the work by Herbst et al. [4] showing that DES intake during pregnancy increases the risk of vaginal clear-cell adenocarcinoma in DES girls. 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.[4] Thirty years later, in 1983, Vessey and his team[5] analyzed the outcomes of these women and their descendants. They discovered that the prevalence of depression and anxiety was twice as high in the girls and boys exposed *in utero* to DES (DES children) than in the placebo group. In 2010, DES deleterious effects on the nervous system were confirmed in the United States of America (USA) by O'Reilly and his team in a large epidemiological study on 76,240 American female nurses, known as the "Nurses' Health Study".[6] In 2016, Soyer-Gobillard et al. analyzed data on 1,002 children from the retrospective HHORAGES cohort among whom 720 were exposed *in utero* to synthetic estrogens. In DES children, they found severe psychotic disorders in post-adolescence that led to numerous suicide attempts and suicides.[7] In 2017, a national survey conducted by Verdoux et al. found that DES women (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.[8] Psychiatric disorders of the same type as those caused by synthetic estrogens have also been observed in children exposed *in utero* to progestins alone[9,10] as well as autism spectrum disorders,[11] in agreement with a study in rats.[12] Moreover, the higher prevalence of male to female transgenderism (1.58% of 253 DES sons) in the HHORAGES-France retrospective cohort and observations from an American cohort suggest that exposure to DES affects also the male sex identity and behavior.[14,15]

Studies on the somatic effects in the second generation (DES daughters and sons) have focused on genital malformations, endometriosis, infertility and cancers. In 2009, Titus-Ernstoff et al in the USA,[16] using data from a large cohort, identified somatic disorders and malformations in DES grandchildren (third generation), such as genitourinary, penile/testicular, skeletal, heart, muscle/tissue, eye and neurological alterations, but without details. In France, Tournaire et al.[17] reported esophageal atresia and premature births in both DES daughters and sons as well as an increased incidence of genital malformations and hypospadias in DES sons, cryptorchidism and penile hypoplasia in third-generation boys.[18-20] Moreover, Gaspari et al. described endometriosis in second- and third-generation DES girls.[21] In addition, in the 62 children from the HHORAGES retrospective cohort exposed *in utero* only to progestins, in addition to psychiatric disorders, various somatic disorders were noted in eight boys (n=2 hypospadias, n=1 absence of urethral meatus, n=1 bilateral mega-ureter, n=2 uni- or bilateral cryptorchidism, n=2 ambiguous genitalia) and ten girls (n=4 hormonal sterility, n=1 tight urethra, n=2 hirsutism, n=1 enuresis, n=1 ambiguous genitalia, n=1 hermaphroditism).[11]

In the present work, we report the congenital musculoskeletal malformations identified in the second- and third-generation descendants of women treated with synthetic estrogens and progestogens during pregnancy (data from the HHORAGES retrospective cohort) and discuss the multigenerational impact of these endocrine disruptors.

2. MATERIAL AND METHODS

As described in a recent paper [22], our data were from the HHORAGES retrospective cohort that includes 1,200 women who were treated with and their children (~2,000; second generation) exposed or not *in utero* to DES and other synthetic estrogens (e.g. 17-α-ethinyl estradiol, EE) and/or progestogens/progestins (e.g. 17-α-hydroxyprogesterone caproate). These individuals completed a detailed medical questionnaire described in a chapter of the book *"State of the Art of Therapeutic Endocrinology"*.[23] The local university hospital [Montpellier University Hospital (CHU Montpellier)] F-34290, Montpellier) ethics committee approved this study (20-04-26) (ID IRB No. 202601532), and all patients gave their informed consent through the HHORAGES-France Association. The data collected through the questionnaires have been used to study the somatic and psychological effects of the synthetic hormones administered during pregnancy. The questionnaire and the use of the collected data for research have been approved by the French National Commission for Information Technology and Liberties (CNIL) (J B/EM/DC042793, N◦ 1006460). As data were de-identified, the informed consent of individual subjects was not required.

3. RESULTS

3.1. Retrospective cohort description

The HHORAGES retrospective cohort includes 1,934 second-generation individuals: 302 unexposed first-born children (154 girls, 148 boys) and 1,225 children exposed to synthetic hormones (n=1,163 exposed to estrogens and/or progestins, among whom 395 only to DES, and n=62 only to progestins) (Figure 1).

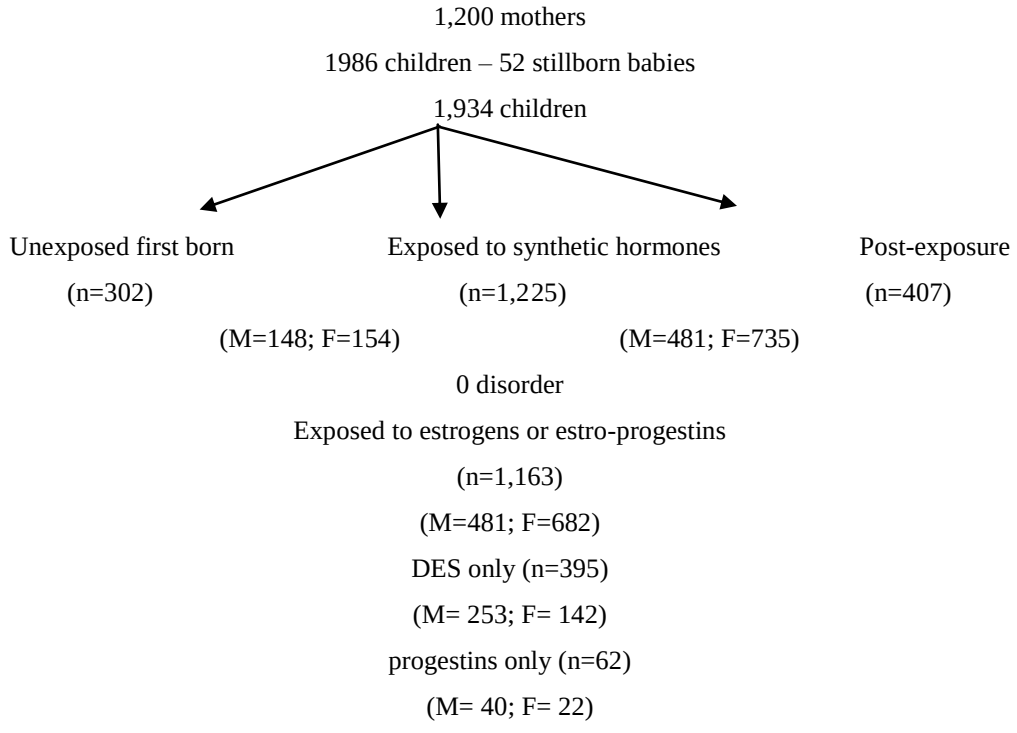

Figure 1: Whole HHORAGES cohort and repartition males (M) and Females (F). HHORAGES-France data.

Concerning DES, the cumulative dose D administered to the French pregnant mothers was 4,050 mg < D < 7,300 mg. As shown by Tournaire et al [23] this is lower compared with the higher doses administered in the USA (7,550 mg < D < 12,742 mg).

3.2. Hormonal treatments

Table 1 shows two representative examples of women treated with DES, EE and 17- α -hydroxyprogesterone caproate, from the beginning to month 8 of pregnancy, in France, between 1966 and 1972. These hormonal treatments were administered by gynecologists/obstetricians to pregnant women with history of miscarriages or difficulties in conceiving.

Table 1: Hormonal treatments administered to two patients from week 7 of amenorrhea to month 8 of pregnancy. HHORAGES-France data.

1- Treatments of Mrs. A. from the beginning to month 8 of pregnancy

First pregnancy (1966)

1 Distilbene®25 mg tablet/day,

1 Ethinyl estradiol Roussel 500 µg tablet/day

1 weekly injection of Progesterone Retard Pharlon 125 mg (17-alpha-hydroxyprogesterone caproate)

Second pregnancy (1969)

1 Ethinyl estradiol Roussel 500 µg tablet/day

1 weekly injection of Progesterone Retard Pharlon 125 mg (17-alpha-hydroxyprogesterone caproate)

Third pregnancy (1972)

1 Ethinyl estradiol Roussel 500 µg tablet/day

1 weekly injection of Progesterone Retard Pharlon 125 mg (17-alpha-hydroxyprogesterone caproate)

Replaced by Luteran 2 tablets/day (chlormadinone acetate, a progestin) from month 5 to month 8 of pregnancy.

2- Treatments of Mrs. B. from the beginning to month 8 of pregnancy

Medical History: 1 miscarriage at 6 weeks of amenorrhea 2 years prior. Normal hysterosalpingography. Deficient hormone levels.

First pregnancy (1967)

At week 7 of amenorrhea: Ethinyl estradiol 100 µg/day (19 µg/kg/day).

From week 10 to week 20: Distilbene® 15 mg/day (288 µg/kg/day) + EE 100 µg/day.

From week 20 to week 37: Distilbene® 15 mg/day + EE 250 µg/day (48 µg/kg/day) + Progesterone Retard Pharlon 500 mg/week (9.6 mg/kg/week). A baby girl was born at term. Apgar score 10/10. No problems during the pregnancy.

Second pregnancy (1971)

At week 6 of amenorrhea: EE 250 µg/day. From week 8 to week 37: EE 500 µg/day + Distilbene® 25 mg + Progesterone Retard Pharlon 500 mg/day. A baby boy was born at term. Apgar score 10/10. No problems during the pregnancy.

Table 2 lists the different progestins administered alone or with estrogens to pregnant women in the HHORAGES cohort. The most prescribed compound was 17-alpha-hydroxyprogesterone caproate. Later, this progestin was banned for use in pregnant women in 2000, but was reauthorized in 2011 [24] to prevent recurrent preterm delivery. Then, it was banned again in the USA in 2022 and in France in 2024 [25], following an American study of more than 18,000 mother-child pairs showing that *in utero* exposure to 17-α-hydroxyprogesterone caproate was associated with pediatric cancer in the offspring.[26]

Table 2: Progestins administered to pregnant women during their pregnancy in the HHORAGES cohort (n=66 women treated only with progestins). The numbers in parentheses represent the number of patients treated with that progestin. HHORAGES data.

Chlormadinone acetate (11)	Withdrawn 1970
17-a-Hydroxyprogesterone heptanoate (13)	Withdrawn 2002
17-alpha-Hydroxyprogesterone caproate (32) (used as progestin delay)	Withdrawn 2000 Reauthorized 2011 Withdrawn 2022 (USA), 2024 (France)
Dydrogesterone (4)	Contraindication
Micronized progesterone (4)	Contraindication
Levonorgestrel (1)	Contraindication
Norethisterone base (1)	Contraindication

3.3. Congenital musculoskeletal malformations in the second- and third-generation children of women treated with synthetic hormones during pregnancy

Questions on musculoskeletal malformations were not specifically included in the questionnaire filled in by the individuals included in the HHORAGES-France cohort; however, these problems were spontaneously mentioned in the framework of the mental health disorders described by the concerned families. Therefore, these findings cannot be considered exhaustive.

3.3.1. Congenital musculoskeletal malformations in prenatally exposed children to xenohormones (second generation)

Ten families mentioned the presence of congenital musculoskeletal anomalies (birth defects) in one or more of their children who were exposed *in utero* to synthetic estrogens (DES or EE) and/or progestins (Table 3).

In six cases, the mother was treated only with DES during pregnancy: the cumulative doses were 4,050 mg < D < 7,300 mg.

- Case 1 (file number in Table 2: 803): Girl born in 1971 with deformed hands (she did not have children);
- Case 2 (1021): Girl born in 1963 with digitigrade gait (no children);
- Case 3 (1021) Girl born in 1967 with agenesis (i.e. failure of an organ or body part to develop, resulting in its complete absence or incomplete development) of the feet (no toes) and both hands (right hand with two fingers, left hand with only the thumb) (three healthy boys);
- Case 4 (1062): Girl born in 1968 with craniosynostosis (i.e. birth defect in which the bones in the baby's skull join too early) (one healthy daughter);
- Case 5 (1131): Boy born in 1968 with total hemimelia (i.e. a congenital malformation characterized by the absence of part or all of a limb) of both arms and hands (two healthy boys);

- Case 6 (1303): Girl born in 1974 with asymmetrical craniosynostosis (no children); In the other four cases, the mother was treated with synthetic estrogens and progestins:
- Case 7 (1095): After prenatal exposure to progestin and EE, boy born in 1978 with muscle hypotonia and psychomotor delay, deformed hands and feet (no children);
- Case 8 (1123): after prenatal exposure to DES and progestins, girl born in 1967 with atrophied right hand and foot (after 11 *in vitro* fertilization cycles, two sons with mental and cognitive disorders);
- Case 9 (1129): After several years of marriage and a failed attempt to conceive, a woman consulted an obstetrician-gynecologist at the University Hospital of Angers (France). After a diagnostic work-up that revealed mild endometrial hyperplasia, bicornuate uterus of small size, and satisfactory sex hormone levels, the physician prescribed a treatment with Lyndiol®, 5mg (EE and the progestin lynestrenol) to be taken every day and for a minimum of 3 months. Lynestrenol is a synthetic progestin, of the nonsteroid type, that acts as an agonist of the progesterone receptor. A pregnancy occurred after three weeks of treatment. An estrogen-progestin treatment was then administered: i) Duphaston® 10 mg (dydrogesterone, a synthetic progestin), 1 tablet morning and evening for 1 month; followed by ii) EE cp 500 (1/2 tablet per day) and Progesterone Retard Pharlon 250 (17-α-hydroxyprogesterone caproate, 1 injection every 5 days) for 1 month; then, iii) Duphaston® 10 mg, 2 tablets morning and evening for 1 month; followed by iv) EE cp 500 (1/2 tablet per day) and Progesterone Retard Pharlon 250 (1 injection every 6 days) until month 8 of pregnancy. Calcium fluoride, Leodrine® (a thiazide diuretic), Lasix® (furosemide, a diuretic), and a salt-free diet were also prescribed. A cesarean section was scheduled for November 24, 1971, as the child was breech. At birth, the child, a boy, weighed 2.85 kg and presented several malformations:
- absence of the left forearm and hand, the left humerus ended in three small bony segments and a finger without a joint,
- right hand with three fingers, including the thumb,
- high arch in the right foot, absence of a toe, and anomaly in the talus and calcaneus bones; difference of four shoe sizes compared to the left foot, making walking difficult,
- shorter bones in all four limbs by ~15 cm,
- hemangioma in the middle of his back (surgically treated),
- phimosis, surgically treated at the age of two years.

Genetic testing was undertaken in 1973 and no chromosomal abnormality was detected.

Anxiety, pathological gambling, and eating disorders necessitated ongoing psychiatric care in his youth. He had a son in 2009, born with bilateral cryptorchidism, which was surgically corrected at the age of two years. No ancestor or descendant in this (large) family has physical or mental abnormalities. In 1977, the mother had a second child (girl) (no intake of estrogens/progestins during this pregnancy). In her late teens, this daughter developed psychiatric disorders, including severe depression and several suicide attempts (no children).

- Case 10 (1153): after prenatal exposure to DES and progestins, boy born in 1973 with deformed hands and feet, major motor disability, unable to walk, wheelchair-bound (no children).

In summary, in the 1,225 children exposed *in utero* to synthetic hormones in the HHORAGES retrospective cohort, four cases of agenesis and hemimelia are particularly striking: agenesis of both feet and hands (case 1021), agenesis of

left forearm and right hand and right foot (case 1129), total hemimelia of both arms and hands (case 1131), and atrophied right hand and foot (case 1153). These cases represent 4/1,225 exposed children (32.65/10,000). Moreover, two children were born with craniosynostosis (2/1,225=16.32/10,000). The other children were born with deformed hand (case 803), digitigrade gait (case 1021), deformed hands and feet, muscular hypotonia (case 1095), and deformed hands and feet and major motor disability (case 1153). Five of them had children (third generation), but none of them was born with congenital musculoskeletal malformations. Table 3 summarizes these data.

Table 3: Congenital musculoskeletal anomalies (in blue) in individuals exposed *in utero* to estrogens and/or progestins (second generation). Data HHORAGES-France.

File number of the family in the HHORAGES retrospective cohort	Birth date of the child(ren) exposed *in utero*	Mother's treatment during pregnancy	Sex of the of the child(ren) exposed *in utero*	Phenotype of the of the child(ren) exposed *in utero*	Grandchildren (phenotype)
803	1971	DES	Female	Severe depression; no ovulation/periods; deformed hands.	No
	1973	DES	Female	Severe depression.	No
1021	1963	DES	Female	Pre-term birth (6 months of pregnancy; digitigrade gait (two surgical operations), wheelchair-bound, obesity.	No
	1967	DES	Female	Foot agenesis of feet (no toes) and hands (right hand with two fingers, left hand with only the thumb).	3 healthy sons
1062	1968	DES	Female	Uterine distortion; craniosynostosis.	1 healthy daughter
	1970	No	Female	No	No
	1973	No	Male	No	No
1095	1968	No	?	No	Two healthy children
	1973	No	?	No	No
	1978	EE + progestins (Gravibinan + Progesterone Retard Pharlon	Male	Bilateral cryptorchidism, micro-penis; strabismus, nystagmus, amblyopia; muscular hypotonia, deformed hands and feet.	No
1123	1967	DES + progestins (Progesterone Retard Pharlon)	Female	Premature birth (7.5 months of pregnancy); small uterus; three nipples; hand atrophy (both).	After 11 IVF attempts, 1 son in 1999 (mental disability) and 1 son in 2000 (hyperactivity).

1129	1971	EE + Duphaston + Progesterone Retard Pharlon	Male	Phimosis (surgery); history of mental health problems; agenesis of the left arm and hand, absence of the 4th and 5th fingers of the right hand, absence of the 5th toe of the right foot, shortening of the remaining limbs by ~15 cm.	Son with bilateral cryptorchidy
	1977	No	Female	Severe depression, suicide attempts	No
1131	1968	DES	Male	Bilateral cryptorchidism (surgery at 12 years of age); agenesis of both arms and hands	2 heathy sons
1153	1967	DES + Progesterone Retard Pharlon	Female	Delusional manic-depressive psychosis; colon cancer (treated)	2 healthy children
	1969	DES + Progesterone Retard Pharlon	Male	Behavioral disorders (death by car accident at 18 years)	No
	1973	DES + Progesterone Retard Pharlon	Male	Behavioral disorders, inguinal hernia, hypogonadism, micro-penis, orchidectomy (right testicle); distorted hands and feet, major motor disability, inability to walk.	No
1303	1974	DES	Female	Schizophrenia; asymmetric craniosynostosis (2 surgical operations)	No

3.3.2. **Congenital musculoskeletal malformations in third-generation children** (Table 4)

We found eight cases of grand-children with musculoskeletal malformations (third generation).

- Case 1 (file number in Table 3: 537): the daughter (second generation), prenatally exposed to DES, has a history of severe depression and anxiety. Her daughter (third generation) was born in 2002 with agenesis of the left hand (no fingers);
- Case 2 (564): the second-generation daughter (prenatal exposure to DES and progestins) had two sons: the first with bilateral cryptorchidism, phimosis and delayed skeletal development and the second with clubfoot and overall developmental delay;
- Case 3 (668): the second-generation daughter (prenatal exposure to DES) reported severe depression, aggression, and suicide attempts. Her first son was born before term (7 months of pregnancy) with clubfoot and craniosynostosis;

- Case 4 (688): the second-generation daughter (prenatal exposure to DES) experienced fertility problems and was treated with the synthetic estrogen clomiphene citrate (Clomid) and/or progestin (Utrogestan) to stimulate ovulation. The boy born in 2001 after treatment with the progestin alone had a malformed foot;
- Case 5 (807): the second-generation daughter (prenatal exposure to DES and progestins) had a malformed uterus and fertility problems and underwent ten *in vitro* fertilization attempts. She had a son with a left foot in which the last toe is mispositioned and two toes are fused, and with protruding floating ribs;
- Case 6 (981): the second-generation son (prenatal exposure to DES and a progestin) has a history of schizophrenia. One of his sons was born with webbed hands;
- Case 7 (1094): the second generation daughter (prenatal exposure to DES) was born before term (6.5 months of pregnancy) with a small T-shaped uterus. She had a son born with legs of different length and craniosynostosis;
- Case 8 (1184): the second-generation son (prenatal exposure to DES), with history of mental health problems, had a daughter born with clubfoot.

In summary, left hand agenesis, clubfoot, webbed hands, craniosynostosis, and leg length discrepancies are the malformations observed in the third generation. Unfortunately, we do not know the total number of third-generation children in our cohort and therefore, we could not calculate the prevalence of musculoskeletal malformations in this group. Table 4 summarizes these data.

Table 4: Congenital musculoskeletal anomalies (in blue) in children of individuals exposed *in utero* to estrogens and/or progestins (third generation). Data HHORAGES-France.

File number of the family in the HHORAGES retrospective cohort	Birth date of the child(ren) exposed *in utero*	Mother's treatment during pregnancy	Sex of the of the child(ren) exposed *in utero*	Phenotype of the child(ren) exposed *in utero*	Grandchildren (year of birth) and phenotype
537	1970 1972	DES DES	Female Female	Severe depression and anxiety. Severe depression.	Daughter (2002): left hand agenesis (no fingers). No
564	1964 1965	DES + progestins (Progesterone Retard Pharlon) DES	Female Male	None Pre-term delivery (5.5 months of pregnancy).	Son (1994): bilateral cryptorchidism, phimosis; delayed skeletal development. Son (1997): clubfoot (both) and overall developmental delay. 2 healthy children
668	1967	DES	Female	Severe depression, aggressivity, many suicide attempts; small uterus	Son (1994): premature birth (7 months of pregnancy); clubfoot (right), craniosynostosis. Son (1997): healthy.

688	1970	DES	Female	Fertility problems	Daughter (1999; after treatment with Clornid + Utrogestan): resuscitated at birth. Son (2001; after treatment with Utrogestan): pre-term delivery (8 months of pregnancy; resuscitation after sudden infant death; hearth problems; distorted left foot.
807	1970	DES + progestins (Utrogestan)	Female	Uterine distortion	After 10 IVF attempts, son (2001) with last toe mispositioned and two fused toes in the left foot, protruding floating ribs.
981	1973 1977 1979	DES + progestins (Tocogestan) DES DES	Male Female Male	Premature birth; schizophrenia (murder). No Phimosis	Son (2000): healthy. Son (2004); webbed hands. Son (2006): healthy. Son (1998): hypospadias (surgical intervention) Son (2004): hypospadias (surgical intervention). No
1094	1961 1967	No DES	Male Female	No. Premature delivery (6.5 months of pregnancy); small T-shaped uterus.	Son Son (1992): premature delivery (5.5 months of pregnancy); unilateral cryptorchidism; schizophrenia, depression; legs of different length (surgery), craniosynostosis.
1184	1970	DES	Male	Bipolar disorder	Daughter (1998): clubfoot (both).

4. DISCUSSION AND CONCLUSION

Limb defects may be related to genetic factors, prenatal exposure to drugs and environmental toxicants. However, the possible limb teratogenicity of thousands environmental factors remain unknown. Placental insufficiency due to altered placental growth and trophoblast invasion is well described; however, xenoestrogens may affect fetal development also through hormone homeostasis, inflammation, oxidative stress and epigenetic changes.[27]

The results of this work, which is not an epidemiological study but is based on the analysis of spontaneous testimonies from the HHORAGES retrospective cohort, suggest that hormonal treatments during pregnancy may have negative effects not only in the progeny directly exposed *in utero* but also on their children. These effects include mental health disorders (extensively described in several previous works),[28,29] genital tract anomalies,[16,18,19] cancers[4,26,30,31] and congenital musculoskeletal malformations ([18] and this work).

It is estimated that in Western countries, ~2-3% of children in the general population are born with a congenital malformation.[32] In the 2021 report by ANSES (French Agency for Food, Environmental and Occupational Health & Safety) (2021),[33] it was estimated that in the French general population, 5.47/10,000 children are born with a congenital limb malformations (agenesis or hemimelia). It has been forecasted that congenital limb agenesis and deficiencies should affect 7.9/10,000 live births in Western countries in 2026,[32] prompting caution in interpreting the first reported observations of congenital musculoskeletal malformations associated with *in utero* exposure to synthetic hormones.

Nevertheless, in the second-generation (children exposed *in utero* to xenohormones), 4 of 1,225 children were born with hemimelia or agenesis of the upper and lower limbs. This represents 32.6/10,000, which is almost 6 times higher than the French general population rate reported in the ANSES report[33] and 4.12 times higher than the rate estimated for 2026 in Western countries [32]. However, we do not believe that these are coincidental occurrences in our patient cohort, despite the bias inherent due to its retrospective nature. For instance, the rate of craniosynostosis (2/1,225 exposed children) is almost four times higher than in the general population (1/2,500), according to information from the European Reference Network on Craniosynostosis and Head and Neck Diseases (www.em-cranio.eu).

Regarding malformations in the third-generation children, agenesis was rare, but craniosynostosis and foot deformities (clubfoot) were more frequent. Unfortunately, we were unable to calculate percentages because we do not know the exact number of grandchildren.

Overall, 5% of all congenital malformations are thought to be the consequence of drugs taken during pregnancy, as specified by the French Reference Center for Teratogenic Agents (CRAT: https://www.lecrat.fr) including DES and thalidomide (a-(N-phthalimido) glutarimide) [34]. In the testimonies collected from the HHORAGES retrospective cohort, pregnant mothers were treated with DES alone, DES + progestins, DES + EE + progestins, EE alone, or EE + progestins (Tables 3 and 4). In all cases, somatic and/or mental health disorders were detected in the children exposed *in utero* (second generation). Conversely, the grandchildren (third generation), derived from germ cells exposed *in utero* [35], were less affected, despite the fact that sometimes, their mothers (second generation) underwent *in vitro* fertilization cycles or received progestins to promote fertility or to support difficult pregnancies.

4.1. Teratogenic mechanism of DES.

From the 1990s, several authors tried to explain the teratogenic mechanism of DES and other xenoestrogens. In 1990, Liehr[27] proposed a plausible mechanism for tumor initiation. Specifically, catecholestrogens and DES are oxidized to semiquinones and quinones by the peroxidatic activity of cytochrome P-450 in animals and humans. These metabolites can bind to DNA. Based on the binding of DES-derived quinone to DNA, this intermediate must be considered as a possible carcinogenic metabolite. Mittendorf[35] confirmed the hypothesis that exposure to DES *in utero* has carcinogenetic and teratogenic effects and suspected “other possible health effects that have not yet been fully

evaluated". Moreover, a possible link with chromosomal abnormalities caused by DES was suggested by de Stoppelaar et al in 2000.[36] However, to our knowledge, the mechanism of these teratogenic effects has not been fully elucidated yet, and may include epigenetic[37] and genetic mechanisms.[36] Our observations lead us to suggest possible angiogenesis defects that hinder the growth of upper or lower limbs in the second- and/or third-generation children. In 2016, in a retrospective cohort study, using self-administered questionnaires (n=3,436 DES-exposed women who had given birth to 6,203 children), Tournaire et al. [18, Table 1] identified different malformation types, including musculoskeletal anomalies (n=20 grand-daughters and n=31 grand-sons). Unfortunately, they did not specify the malformation types, but for clubfoot and omphalocele (i.e. failure of abdominal wall closure, not observed in our cohort). Similarly, in 2022, Epelboin et al[38] reported musculoskeletal malformations in DES-exposed families, but without further details.

4.2. Teratogenic mechanism of EE

Caston's group[39,40] demonstrated that rats exposed *in utero* to 17-α-ethinyl estradiol develop anxiety- and depressive-like behaviors. *In vitro* and *in vivo* assays showed EE clastogenic effect, causing DNA strand breakages or chromosome aberrations in human lymphocyte cultures [41]. Although EE has been banned in Europe for pregnant women since 1980, it is one of the major components of the contraceptive pill. In 2019, Meyer et al[42] showed in mice, the severe consequences on fetal growth and survival depending on the 17-α-ethinyl estradiol dose. Exposure to this synthetic estrogen affects placenta growth and angiogenesis, even at low dose (0.005 μg/kg body weight/day), and also spiral artery remodeling.[43] Based on these findings, the authors urged to identify the mechanisms that are deregulated after exposure to estrogens. This work was later confirmed[44] by Ramirez-Montero et al. who analyzed 17-α-ethinyl estradiol effects on embryo development and oxidative stress biomarkers in the zebrafish *Danio rerio*. They found that it was teratogenic, leading to chorda malformation, small fin and developmental delay.

4.3. Teratogenic mechanism of progestins

After the banning of estrogens, such as DES in 1977 and EE in 1980, only exogenous progesterone remained for the management of patients with infertility, hypoestrogenism and secondary amenorrhea.[45] Moreover, it is prescribed for luteal phase maintenance in assisted reproduction programs and during pregnancy for the management of threatened miscarriage, recurrent miscarriage and preterm labor risk.[46] In a recent work,[47] Danielsson et al. reviewed studies published between 2014 and 2023 on the teratogenic effects of the "estrogen-progestin pregnancy tests" (HPT). These tests contained synthetic estrogen and progesterone and were used to detect pregnancy from the 1950s to the early 1980s. Analyzing human and animal studies, they showed that this estrogen-progestin mixture caused limb reductions, neural tube defects, and urinary-renal system defects in the fetus, as well as vascular disruption in the embryo, secondary to compression of uterine/embryonic vessels. They likened its mode of action to that of misoprostol, a synthetic analogue of prostaglandin E1, with potential abortive and teratogenic effects. Experiments in Albino rats showed that the administration of exogenous progesterone (1.8 and 3.6 mg/200 g body weight) in pregnant animals affects fetal growth, skeletal construction, and sex organ development.[48]

The tragedy of DES and other hormones inevitably brings to mind that of thalidomide, the most studied teratogen in humans, which has been associated with an increased risk of malformations, from 20 to 50%. Thalidomide mechanisms of action are now well understood and are multiple, combining immunomodulatory and cytokine-modulatory effects and especially angiogenesis inhibition.[49] Preventing the growth of new vessels in a developing limb deprives

proliferating cells of essential nutrients, leading to decreased proliferation and the subsequent reduction in the overall limb size. Paradoxically, the discovery of its mechanism of action, especially its antiangiogenic functions, have allowed repositioning thalidomide for the treatment of type II leprosy, in oncology and hematology.

In describing the various effects of synthetic sex hormones on children exposed *in utero*, one similarity in their mechanism of action with that of thalidomide can be noted, particularly concerning the angiogenesis defect caused, for instance, by EE[42] and by estrogen-progestogen combinations[44,47] as well as those observed in this work. Previous observations by Tournaire et al. in 2016 [18], despite their lack of precision on musculoskeletal abnormalities, suggest that DES influences the occurrence of these abnormalities in DES grandchildren, a finding confirmed by our own observations (agenesis, clubfoot, craniosynostosis). However, molecular studies are very rare and more investigations are needed to better understand the mechanisms of action on the fetus and its offspring. The extensive data now available on the xenoestrogen DES and other synthetic hormones indicate that they act as endocrine disruptor chemicals,[12,50,51] causing both psychiatric and somatic effects in the individuals directly exposed and also in their progeny. Indeed, in the exposed second-generation population, the percentage of children with agenesis is six times higher than in the French general population, demonstrating a direct link with the administration of these xenohormones during pregnancy. Moreover, the third generation is not spared. Importantly, the third-generation children often experienced the effects of a double exposure: i) the germ cells of the fetus (one of their future parents) who was exposed *in utero*,[35] and ii) the hormonal treatment based on progestins taken by their mother (second generation) in case of fertility/pregnancy problems. This is extremely worrying because the descendants of women treated with DES represent more than 50 million people worldwide.[51] Therefore, the exposure to exogen sex hormones and other widespread endocrine disruptors might negatively affect (and will affect) the life of hundreds of millions people worldwide.

Author Contributions: Conceptualization, M.-O.S.-G., L.G-S. and C.S.; methodology, M.-O.S.-G. and C.S.; validation, formal analysis, C.S.; investigation, M.-O.S.-G. and C.S.; resources, M.-O.S.-G.; data curation, C.S.; writing—original draft preparation, writing—review and editing, M.-O.S.-G.; visualization, supervision, C.S.; project administration, M.-O.S.-G.; funding acquisition, no matter. All authors have read and agreed to the published version of the manuscript.

Funding: No matter.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of CHU Montpellier Pole 0078 Femme Mère Enfant protocol code 202301531/9-11-2023.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study via the Association Hhorages-France.

Data Availability Statement: Data are contained within the article.

ACKNOWLEDGMENTS

The authors warmly acknowledge families of HHORAGES-France for their participation in answering self-report questionnaires and interviews and analyses. This work could not continue without the daily ongoing support of the

HHORAGES-France board. (HHORAGES-France, a patient association, is registered at the Epidemiological Portal of French Health Databases INSERM (French National Institute for Medical Research) and AVIESAN (National Alliance for Life Sciences and Health) (epidemiologiefrance.aviesan.fr). The authors also thank Elisabetta Andermarcher for corrections and relevant suggestions for the manuscript.

Conflicts of Interest

M-OS-G is a researcher and President of the HHORAGES-France Association (Unpaid) 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.

REFERENCES

1. Dodds E, Goldberg L, Lawson W, Robinson R. Oestrogenic activity of certain synthetic compounds. Nature, 1938; 141: 247–248. https://doi.org/10.1038/141247b0.
2. Lacassagne A. The appearance of mammary adenocarcinomas in male mice treated by a synthetic estrogenic substance. Week Rep Soc Biol Affil, 1938; 12: 641–643.
3. Dieckmann WJ, Davis ME, Rynkiewicz LM, Pottinger RE. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? Am J Obstet Gynaecol, 1953; 66: 1062-1081. DOI: 10.1016/s0002-9378(16)38617-3
4. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. New England J of Medicine, 1971; 284(15): 878-881. DOI: 10.1056/NEJM197104222841604
5. Swyer GIM, Law RG. An evaluation of the prophylactic ante-natal use of Stilboestrol. Preliminary report. J Endocrinol, 1954; 10: vi.
6. Vessey MP, Fairweather DV, Norman-Smith B, Buckley J. A randomized double-blind controlled trial of the value of stilboestrol therapy in pregnancy: long-term follow-up of mothers and their offspring. Br J Obstet Gynecol, 1983; 90: 1007-1017. DOI: 10.1111/j.1471-0528.1983. tb06438.x
7. O'Reilly ÉJ, Mirzaei F, Forman MR, Ascherio A. Diethylstilbestrol Exposure in Utero and Depression in Women. Am J Epidemiol, 2010; 171: 876-882. https://doi.org/10.1093/aje/kwq023
8. Soyer-Gobillard MO, Paris F, Gaspari L, Courtet Ph, Sultan Ch. Association between fetal DES-exposure and psychiatric disorders in adolescence/adulthood: evidence from a French cohort of 1,002 prenatally exposed children. Gynecol Endocrinol, 2016; 32(1): 25-29. https://doi.org/10.3109/09513590.2015.1063604
9. Verdoux H, Devouche E, Tournaire M, Levadou A. Impact of prenatal exposure to diethylstilbestrol (DES) on psychological outcome: a national survey of DES daughters and unexposed controls. Archivs of Womens Mental Health, 2017; 20(3): 389–395. DOI : 10.1007/s00737-016-0711-8
10. Soyer-Gobillard MO, Puillandre M, Paris F, Gaspari L, Courtet Ph, Sultan Ch. Neurodevelopmental disorders in children exposed in utero to synthetic progestins: analysis from the national cohort of the Hhorages Association*. Gynecological Endocrinology, 2019; 35(3): 247–250. https://doi.org/10.1080/09513590.2018.1512968
11. Soyer-Gobillard MO, Gaspari L, Yao P, Sultan C. In: Martin C and Rajendram P V (eds.). Factors affecting neurodevelopment. Elsevier/Academic Press: London: 2021; pp. 395–408. https://doi.org/10.1016/B978-0-12-817986-4.00034-1.

12. Zou Y, Lu Q, Zheng D, Chu Z, Liu Z, Chen H, Ruan Q, Ge X, Zhang Z, Wang X, Lou W, Huang Y, Wang Y, Huang X, Liu Z, Xie W, Zhou Y, Yao P. Prenatal levonorgestrel exposure induces autism-like behavior in offspring through ERβ suppression in the amygdala, Mol Autism, 2017; 8: 1–16. https://doi.org/ 10.1186/s13229-017-0159-3.
13. Li L, Li M, Lu J, Ge X, Xie W, Wang Z, Li X, Li C, Wang X, Han Y, Wang Y, Zhong L, Xiang W, Huang X, Chen H, Yao P. Prenatal progestin exposure is associated with autism spectrum disorders, Front Psychol, 2018; 9: 1–12. https:// doi.org/10.3389/fpsyt.2018.00611.
14. Gaspari L, Soyer-Gobillard M-O, Kerlin S, Paris F, Sultan Ch. Early Female Transgender ldentity after Prenatal Exposure to Diethylstilbestrol: Report from a French National Diethylstilbestrol (DES) Cohort J Xenobiot, 2024; 14(1): 166-175. Doi: 10.3390/jox14010010.
15. Troisi R, Palmer JR, Hatch EE, Strohsnitter WC, Huo D, Hyer M, Fredriksen-Goldsen KI, Hoover R, Titus L. Gender ldentity and Sexual Orientation ldentity in Women and Men Prenatally Exposed to Diethylstilbestrol. Arch Sex Behav, 2020; 49(2): 447-454. Doi: 10.1007/s 10508-020-01637-7. Epub 2020 Jan 23.
16. Tournaire M, Epelboin S, Devouche E. Histoire du diéthylstilbestrol. Thérapie 2014; 69(1):101–114. https://doi.org/10.2515/therapie/2014012
17. Titus-Ernstoff L, Troisi R, Hatch EE, Palmer JR, Hyer M, Kaufman R, Adam E, Noller K, Hoover RN. Birth defects in the sons and daughters of women who were exposed in utero to Diethylstilbestrol (DES). Internat J of Andrology, 2010; 33(2): 377–384. doi:10.1111/j.1365-2605.2009.01010.x
18. Tournaire M, Epelboin S, Devouche E, Viot G, Le Bidois J, Cabau A, Dunbavand A, Levadou A. Adverse health effects in children of women exposed in utero to diethylstilbestrol (DES). Therapie, 2016; 71(4): 395–404.
19. Tournaire M, Devouche E, Epelboin S, Cabau A, Dunbavand A, Levadou A. Birth defects in children of men exposed in utero to diethylstilbestrol (DES). Therapie, 2018; 73(5): 399-407. https://doi.org/10.1016/j.therap.2018.02.007
20. Wautier A, Tournaire M, Devouche E, Epelboin S, Pouly JL, Levadou A. (2019). Genital tract and reproductive characteristics in daughters of women and men prenatally exposed to diethylstilbestrol (DES). Therapie, 2020; 75(5): 439-448. doi: 10.1016/j.therap.2019.10.004. Epub 2019 Nov 1
21. Soyer-Gobillard M-O, Gaspari L, Sultan Ch. Is in utero exposure to female xenohormones harming the neurodevelopment of children and grandchildren? A french national experience and other lessons from the past. World Journal of Pharmaceutical Science and Research, 2025; 4(3): 8-19. CC BY-NC 4.0
22. Soyer-Gobillard MO, Sultan Ch. Behavioral and Somatic Disorders in Children exposed *in utero* to Synthetic Hormones: A Testimony-Case Study in a French Family Troop. *ln: "State of the Art of Therapeutic Endocrinology"*, Sameh Magdeldin Ed, Niigata University, Japan. lnTechOpen, 2012; pp. 67-86.
23. Tournaire M, Devouche E, Epelboin S, Cabau A. Diethylstilbestrol exposure: evaluation of the doses received in France. Eur J Epidemiol, 2012; *27*: 315–318. DOI 10.1007/s10654-012-9677-7
24. Nelson DB, Herrera Ch, McIntire DD, Cunningham FG. The end is where we start from: withdrawal of 17-alpha-hydroxyprogesterone caproate to prevent recurrent preterm birth. Am J Obst Gynecol, 2024; 1-9. https://doi.org/10.1016/j.ajog.2023.08.031
25. French National Medicine Safety Agency (ANSM). Suspension des autorisations de mise sur le marché des médicaments contenant du caproate d'hydroxyprogestérone. (Suspension of marketing authorizations for medicinal products containing 17-alpha hydroxyprogesterone caproate), August 23, 2024.

26. Murphy CC, Cirillo PM, Krigbaum NY, Cohn BA. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol, 2022; 226(1): 132.e1-132.e14. Doi: 10.1016/j.ajog.2021.10.035. Epub 2021 Nov 9.
27. Liehr JG. Genotoxic effects of estrogens. Mutation Research/Reviews in Genetic Toxicology, 1990; 238(3): 269-276. https://doi.org/10.1016/0165-1110(90)90018-7
28. Kioumourtzoglou MA, Coull BA, O'Reilly EJ, Ascherio A, Weisskopf MG. Association of exposure to diethylstilbestrol during pregnancy with multigenerational neurodevelopmental deficits. JAMA Pediatr, 2018; 172: 670–677. https://doi.org/10.1001/jamapediatrics.2018.0727.
29. Soyer-Gobillard M-O, Gaspari L, Paris F, Kalfa N, Hamamah S, Courtet Ph, Sultan Ch. Prenatal contamination by DES and multigenerational transmission of psychiatric disorders in an informative family. International Journal of Environmental Research and Public Health 2021; 18: 9965. https://doi.org/10.3390 /ijerph 1819996.
30. Hom M, Sriprasert I, Ihenacho U, et al. Systematic Review and Meta-analysis of Testicular Germ Cell Tumors Following In Utero Exposure to Diethylstilbestrol. JNCI Cancer Spectr, 2019; 3(3): pkz045. doi: 10.1093/jncics/pkz045 [PubMed : 31555759]
31. Troisi, R. ; Hatch, EE. ; Titus, L. ; et al. Prenatal diethylstilbestrol exposure and cancer risk in women. *Environ Mol Mutagen*, 2019; 60(5): 395–403. Doi: 10.1002/em.22155 [PubMed: 29124779]
32. Bai Z, Han J, An J, Wang H, Du X, Yang Z, Mo X. The global, regional, and national patterns of change in the burden of congenital birth defects, 1990–2021 : an analysis of the global burden of disease study 2021 and forecast to 2040. eClinicalMedicine November, 2024; 77: 102873. https://doi.org/10.1016/j.eclinm.2024.102873
33. ANSES (French Agency for Food, Environmental and Occupational Health & Safety). First report on transverse upper-limb deficiencies (TULD), 2021; 1-240. https://www.anses.fr/system/files/RAPPORTATMS30092021.pdf
34. Woolf AD. Thalidomide tragedy 1950s. In: Chap 2.4. History of Modern Clinical Toxicology, 2022; 165-175. History of Toxicology and Environmental Health, Academic Press (Elsevier).
35. Shahidhenia M. Epigenetic Effects of Endocrine Disrupting Chemicals. J Environ Anal Toxicol, 2016; 6(4): 1-31. DOI: 10.4172/2161-0525.1000381Mittendorf R. Teratogen update: carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) in utero. Teratology 1995; 51(6): 435-445. https://doi.org/10.1002/tera.1420510609
36. de Stoppelaar JM, Faessen P, Zwart E, Hozeman L, Hodemaekers H, Mohn GR, Hoebee B. Isolation of DNA probes specific for rat chromosomal regions 19p, 19q and 4q and their application for the analysis of diethylstilbestrol-induced aneuploidy in binucleated rat fibroblasts. Mutagenesis, 2000; 15(2): 165–175. https://doi.org/10.1093/mutage/15.2.165
37. Rivollier F, Chaumette B, Bendjemaa N, Chayet M, Millet B, Jaafari N, Barhdadi A, Lemieux Perreault LP, Provost S, Dube MP, Gaillard R, Krebs MO, Kebir O. Methylomic changes in individuals with psychosis, prenatally exposed to endocrine disrupting compounds: Lessons from diethylstilbestrol. PloS One, 2017; 12(4): 1–18. https://doi.org/10.1371/journal.pone.0174783. e0174783.
38. Epelboin S, Tournaire M, Devouche E. Prenatal diethylstilbestrol exposure: transgenerational transmission of adverse effects. Médecine de la Reproduction, 2022; 24(1): 37-48. doi : 10.1684/mte.2022.0875.
39. Dugard ML, Tremblay-Leveau H Mellier D Caston J. Prenatal exposure to ethinylestradiol elicits behavioral abnormalities in the rat. Dev Brain Res 2001; 129(2): 189-199. https://doi.org/10.1016/S0165-3806(01)00205-X

40. Arabo A, Lefebvre M, Fermanel M, Caston J. Administration of 17α-ethinylestradiol during pregnancy elicits modifications of maternal behavior and emotional alteration of the offspring in the rat. Dev Brain Res., 2005; 156(1): 93-103. https://doi.org/10.1016/j.devbrainres.2005.02.003
41. Hundal BS, Dhillon VS, Sidhu IS. Genotoxic potential of estrogens. Mutat Res, 1997; 389(2-3): 173-81. doi: 0.1016/s1383-5718(96)00144-1.
42. Meyer N, Santamaria CG, Müller JE, Schumacher A, Rodriguez HA, Zenclussen AC. Exposure to 17α-ethinyl estradiol during early pregnancy affects fetal growth and survival in mice. Environmental Pollution, 2019; 251: 493-501 https://doi.org/10.1016/j.envpol.2019.04.144
43. Whitley GStJ, Cartwright JE. Cellular and Molecular Regulation of Spiral Artery Remodelling: Lessons from the Cardiovascular Field. Placenta, 2010; 31: 465-474. doi:10.1016/j.placenta.2010.03.002
44. Ramírez-Montero MC, Gómez-Oliván LM , Gutiérrez-Noya VM, Orozco-Hernández JM, Islas-Flores H, Elizalde-Velázquez GA, SanJuan-Reyes N, Galar-Martínez M. Acute exposure to 17-α-ethinylestradiol disrupt the embryonic development and oxidative status of *Danio rerio*. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 2022; 251: 109199 https://doi.org/10.1016/j.cbpc.2021.109199
45. Warren MP, Shantha S. Uses of progesterone in clinical practice. Int J Fertil Womens Med, 1999; 44(2): 96-103. Corpus ID: 42003370.
46. Di Renzo GC, Rosati A, Mattei A, Gojnic M, Gerli S. The changing role of progesterone in preterm labour. BJOG: an International Journal of Obstetrics and Gynaecology, 2005; 112(Supp.1): 57–60. https://doi.org/10.1111/j.1471-0528.2005.00586.
47. Danielsson BR, Ritchie HE. Hormone Pregnancy Tests Were Teratogenic by the Same Failed Abortion and Hypoxia-Related Mechanism as Misoprostol. Birth Defects Research, 2025; 117: e2462 1-22. https://doi.org/10.1002/bdr2.2462
48. Tag HM, Elgawish RA, Ebaid HM, Abdel-Rahman M, Abdelrazek HMA. Prenatal exposure to exogenous progesterone adversely affects fetal development in Albino rats. The Journal of Basic and Applied Zoology, 2021; 82: 16 https://doi.org/10.1186/s41936-021-00212-3
49. Leleu X, Micol JB, Guieze R, Berthon C, Kuhnovsky F, Terriou L, Moreau AS, Yakoub-Agha I, Bauters F, Facon T. Thalidomide : mechanisms of action and new insights in hematology. La Revue de Médecine Interne, 2005; 26(2): 119-127. https://doi.org/10.1016/j.revmed.2004.06.017
50. Robotti S. The heritable legacy of diethylstilbestrol: a bellwether for endocrine disruption in humans. Biol Reprod, 2021; 105(3): 687-689. https://Doi: 10.1093/biolre/ioab146.
51. Sultan Ch, Gaspari L, Soyer-Gobillard M.-O. Effects of endocrine disrupting chemicals in the brain: the example of neurodevelopment alterations upon exposure *in utero* to synthetic sex hormones. J Xenobiot, 2025; 15: 162. https://doi.org/10.3390/jox15050162