Afssaps Agence française de sécurité sanitaire des produits de santé
French Agency for the Safety of Health Products

Complications related to *in utero* exposure to diethylstilbestrol (DES)

(Distilbène®, Stilboestrol-Borne®)

2011 Update

Key facts

The problems associated with *DES* exposure *in utero* remain current and monitoring of the next generation (children of parents exposed *in utero*) must continue to assess the multi-generational effects.

The major role of physicians and particularly gynecologists and obstetricians is to:

- **Inform women who may be affected either because of DES drug treatment during their pregnancy, or because of known exposure to DES *in utero.***

- **Consider *in utero* exposure:**
  1. **when taking the medical history of any woman born between 1948 and 1977, whose mother had miscarriages or obstetrical problems.**
  2. **during clinical examinations when there are characteristic vaginal or cervical lesions**
  3. **where hysterography shows images suggestive of a T shaped uterus or uterine hypoplasia.**

- **Routinely explore possible *in utero* DES exposure in the following clinical situations: a fertility checkup, an ectopic pregnancy, recurrent 1st trimester miscarriages and particularly after any 2nd trimester miscarriage, a premature delivery.**

- **Refer the patient to a DES knowledgeable specialist and arrange for appropriate monitoring when DES exposure is known or suspected.**

- **In principle, consider the pregnancy of a women who has been exposed to DES *in utero* as a high risk pregnancy**

Patients exposed to DES have a crucial role in handing down the "record" of their exposure to the next generations to allow continued adequate monitoring and implementation of appropriate treatment and care.

Historical facts

Diethylstilbestrol (DES), a non-steroidal synthetic estrogen, was prescribed in France between 1948 and 1977, under the trade names Distilbène® and Stilboestrol-Borne® for pregnant women in order to prevent miscarriages, bleeding, as well as other complications during pregnancy such as preeclampsia or pregnancy diabetes.

It is in the USA in 1971 that the first cases of vaginal cancer were discovered among daughters exposed *in utero* to DES. One of the first French cases of vaginal adenocarcinoma among young girls was published in 1975. In France the indication "repeated miscarriages" was withdrawn in 1976 and the contraindication for pregnant women was added in 1977.

Since then, other genital and obstetrical complications associated with *in utero* exposure have been observed and have been successively published, including in brochures distributed to health professionals and then to the general public.

Diethylstilbestrol (DES) is currently marketed under the name Distilbène®, but its only indication is during the medical treatment of prostate cancer.

Current issues

The problems associated with *in utero* DES exposure are still current and probably will remain so for years to come. Indeed, between 1948 and 1976, approximately 200,000 women in France were treated with DES during their pregnancies, with a peak of prescriptions at the end of the 1960's and beginning of 1970's. Taking into account the miscarriages and fetal and neonatal deaths, the number of children born from these pregnancies is estimated at 160,000 (that is 80,000 daughters and 80,000 sons exposed *in utero* to DES). The patients exposed *in utero* are now between 33 and 63 years old, and monitoring the effects of DES exposure for them must continue for years to come, as well as for the children of this population to evaluate the multi-generational impacts.

New scientific information is available since the first DES warning Bulletin was published in January 1983, prepared in collaboration between the association Réseau D.E.S. France and the Affsaps (French Agency for the Safety of Health Products).

Moreover, a recent Afssaps survey among gynecologists revealed that only half of them knew precisely all the adverse effects of DES exposure and that 40% of them hoped that a new information campaign will be organized.

As a result, the Affsaps has decided to update their information Bulletin and to undertake an awareness campaign among health professionals about the methods of DES screening and the follow-up protocols for these patients.

What are the risks associated with an *in utero* exposure to DES ?

The risks of genital damage after DES exposure depends mainly on the period of exposure to the drug treatment rather than its duration or doses. The identified period of risk is between the 6th and 17th week of gestation.

The main established complications that are known are :

For a daughter:

- **Clear cell adenocarcinoma of the vagina and cervix** with an occurrence rate of approximately 1 case per thousand patients exposed *in utero.* An adenocarcinoma has been diagnosed among women aged between 7 and 49 years old, with an average age of 24 ½ years. The declared cases of uterine and vaginal cancers among DES exposed women have considerably decreased since 2005.

**Nevertheless, it is important to continue medical supervision and to note that the proportion of vaginal cancers is diminishing, whereas the number of cervical cases is increasing.

- **Structural, morphological and functional abnormalities of the vagina, cervix and fallopian tubes. In order of frequency they are:**

- *Adenosis (cervico-vaginal ectopy of the cylindrical mucous membrane)*: presence of the cylindrical cervical mucus outside its normal localization. This is observed in about 30% of exposed young women with no symptoms, and in 60% of exposed young women with specific clinical indications. Generally the recovery is spontaneous. The adenosis lesion is likely to bleed and become infected and can be made worse by abusive cervical treatment interventions (coagulation, cryotherapy and laser);

- *Other cervico-vaginal anomalies* (20% to 60% of the young exposed women): structural cervical and vaginal anomalies can be observed. The most frequent is cervical hypoplasia (absence or small tip of the cervix, a 'crest of helmet' appearance);

- *Anomalies of the uterus*: often associated to the former anomalies with, by decreasing order of frequency: a T shaped uterus and small uterine cavity, uterine hypoplasia (uterus globally small), narrowing of the uterine cavity (pseudosynechia), strictures, uterine diverticula;

- *Anomalies of the fallopian tubes*: particularly narrow tubes, as observed by laparoscopy.

- Some of these affects can cause fertility problems (for about one out of three women exposed) and obstetrical complications:

- *ovulation problems* : risk of premature ovarian failure (POF), according to observations, but not yet confirmed

- *cervical problems* with anomalies of the cervical mucus, making sperm penetration difficult

- *ectopic pregnancies* : the risk, compared to the general population, is multiplied 5 or 10 fold, according to different surveys

- *early miscarriages (during the 1st trimester)* : slightly more frequent than in the general population

- *late miscarriages from 15 to 24 weeks gestation* : particularly characteristic among these patients, with 10 times the risk compared to the general population

- *premature births* : related to uterine anomalies

- *postpartum hemorrhage* : the risk is increased in the DES exposed population.

It is to be noted that the percentage of term delivery is 84% for the general population, compared to 50% for DES exposed women, and only 33% for DES exposed women with a morphological genital anomaly.

For the medical care and treatment of genital anomalies in DES exposed women, the following have been suggested:

- Hysteroplasty for enlargement of the uterine cavity with the objective of improving fertility and reducing the risks of recurrent miscarriages. This surgical procedure is not the first-line of management (2003 ANAES recommendations), as its efficacy and safety are not well assessed

- Cervical cerclage in the case of a high risk of late miscarriage or premature birth (with previous history of this type of dysfuncion, or uterine or cervix malformation such as hypoplasia), to be considered on a case by case basis.

For a son:

The adverse urogenital effects of DES exposure *in utero* for a son are more frequent than in the general population, and include epididymal cysts, testicular abnormalities such as hypotrophy of the testes, cryptorchidism, capsular induration and abnormal position of the urinal meatus (hypospadias).

Beyond the known complications of *in utero* exposure:

Different publications have issued warnings of the risk of breast cancer for DES daughters exposed *in utero* but the results of the studies are contradictory.

An American study suggests an increased risk of breast cancer among women DES exposed *in utero* more that 40 years old, with a dose-effect relationship. However, a recent European study does not indicate a significant increase in this risk.

Confronted with these contradictory elements, Afssaps has asked a group of expert epidemiologists to analyze the available information and give their recommendations concerning the relevance of specific supervision measures for *in utero* exposed women. The benefits from mammography screening must be weighed against the risk from X-ray exposure after repeated mammograms.

Patient groups have raised concern about possible occurrence of post-adolescent psychiatric disorders but the study undertaken by Afssaps has not confirmed this risk

Afssaps implemented and funded a study in 2002, coordinated by the Inserm (National health and medical research institute), with a cohort of 1,352 mothers, members of the teachers' health service, and who were DES exposed during at least one of their pregnancies. The study compared the occurrence of recognized serious adult psychiatric disorders (psychiatric hospitalization, suicide) among brothers and sisters exposed with those non-exposed to DES *in utero*, or to progestagens or other hormones. The same results were observed for psychiatric disorders as defined on a broad level, grouping together serious recognized psychiatric disorders as well as medical consultations for psychiatric symptoms.

Recently, results of a USA group study published in "Nurse Health Study", suggest an increase in depression risk associated with DES *in utero* exposure, but there exists a bias notably concerning the method of collecting data on DES exposure and concerning the depressive problems, which limits the validity of these results.

Some patients remain strongly concerned on this matter, and so Afssaps later this year plans to conduct a public hearing for these groups and their experts to reexamine their facts.

What are the risks for the children of parents exposed to DES *in utero* ?

The problems observed among the children of mothers exposed *in utero* are mainly related to the complications associated with premature births.

In addition, certain epidemiological studies, including Dutch and French, have reported an increased risk of hypospadias for sons whom mothers have been exposed to DES *in utero*. As a result, a study has been undertaken by Afssaps, coordinated by the Paris hospital teams (Assistance Publique – Hopitaux de Paris) and by the Inserm (National health and medical research institute) for all the DES *in utero* exposed women having given birth to a son between 1996 and 2008 in the Saint-Vincent-de-Paul maternity hospital in Paris. For now, the identification of cases of hypospadias in the 3rd generation of DES exposed families underlines the necessity to continue monitoring the multi-generational risks of urogenital malformations.

To date, there is no evidence of genital anomalies for the daughters of *in utero* exposed mothers. However, further studies are necessary to confirm these results.

How to screen for DES exposure ?

In cases where DES exposure is known by the mother or by her daughter:

*Either a mother may reveal that she received DES treatment during one or more of her pregnancies between 1948 and 1977. It is necessary to inform her of the possible consequences for her children and to advise her to send them, particularly if they are daughters, to a DES knowledgeable specialist for routine medical follow-up.

*Or a young woman, knowing her DES *in utero* exposure, consults for a gynecological or obstetrical reason. It is necessary to inform her of the risks and to refer her to a DES knowledgeable specialist for routine medical follow-up.

In cases where exposure is unknown:

Confirmation or indicators of *in utero* exposure can be obtained with the following:

1) In questioning a patient born between 1948 and 1977, when learning of the mother's history of miscarriages or obstetrical difficulties.

2) During clinical examination, discovering cervical or uterine anomalies characteristic of a DES exposure.

3) With hysterography, when the images show signs of a DES exposure.

*Moreover, for all women born before 1977, a DES exposure must be routinely explored in the following clinical situations:

- ectopic pregnancies
- recurrent 1st trimester miscarriages, and particularly 2nd trimester miscarriages
- premature births

If DES exposure is suspected, the patient will be referred to a DES knowledgeable specialist for medical follow-up.

What is the routine medical follow-up for women DES exposed *in utero* ?

Even in the absence of any symptom, a yearly consultation with a gynecologist is essential and must include:

*a gynecological examination to check any vaginal or uterine anomaly

*vaginal and cervical smears

*a colposcopy pending on the results of the vaginal and cervical smear tests

Unexplained bleeding between menstrual periods must be immediately followed up with a gynecological examination to eliminate any DES complications.

Recommendations for fertility problems of a woman DES exposed *in utero*

In the case of fertility problems, the medical checkup must include a Huhner test to judge the quality of the cervical mucus, a hysterography to detect an anomaly of the uterine cavity and fallopian tubes and an echography coupled if possible with a Doppler to evaluate the uterine artery pulsatility and thus the possibilities of implanting an embryo.

In all cases, this checkup is included in the general regime for couples with fertility problems.

What pregnancy care for a woman DES exposed *in utero* ?

Every pregnancy for a woman DES exposed *in utero* must be considered, in principle, a high risk pregnancy, even if in many cases it continues normally.

It is recommended that these women be informed of the increased risk of ectopic pregnancies, early and late miscarriages, and premature births, often without feeling contractions.

It is therefore necessary to check on the intra-uterine status of the embryo and to do two-weekly cervical checks.

Preventive measures: resting, reducing activity, stopping work, midwife follow-up at home, possibility of hospitalization – these measures will vary according to the obstetrical history, detected uterine anomalies, and condition and progress of the cervix.

In general, early resting is recommended as the risk of prematurity is approximately the same as for a twin pregnancy. Resting is one of the main factors in preventing miscarriages and prematurity. The French National Health Service has organized exceptional maternity leave (*) for pregnancies related to an exposure to Distilbène®.

Cervical cerclage may be indicated in certain cases.

(*)http://www.ameli.fr/employeurs/vos-demarches/conges/le-conge-maternite/grossesse-pathologique-liee-au-distilbene.php

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(for the references of the regional pharmacovigilance centers, consult the Afssaps site : http://afssaps.fr)

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