

Influence of the Environment on Female Gonadal Function

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Human fertility can be affected by:

- ✓ Genetic abnormalities
- ✓ Endocrine alterations
- ✓ Infectious diseases
- ✓ Exposure to environmental pollutants
(e.g. xenobiotic and heavy metals)

Chemical compounds that may influence female fertility:

ENDOCRINE DISRUPTORS

They are a group of chemical substances (pesticides and industry-related substances) that are potential endocrine disruptors (ED) since they alter the functionality of the endocrine system, affecting the health of an organism or its progenie or of a sub-population.

(European Workshop on the Impact of Endocrine Disruptors on Human Health and Wildlife, Weybridge 2-4/12/1996)

ENDOCRINE DISRUPTERS (ED)

- ✓ They are susceptible to bio-accumulation
- ✓ They can pass thorough the placenta and are present in breastmilk
- ✓ Children are the highest exposed subjects since they are in contact with the EDs for a longer “lifetime”.

EDs with estrogenic or androgenic activity (pesticides, phytoestrogens, phthalates)

In **women**:

- Early puberty
- ✂ ↑ miscarriages
- ✂ ↓ fertility
- Ovulation suppression or delay
- ✂ ↓ of the diameter preovulatory follicle
- ✂ ↑ incidence of ovarian tumours
- Early menopause

In **man**:

- ✂ ↑ incidence of malformations
- ✂ ↑ incidence of testicular tumours
- ✂ ↓ reproductive capability

The main chemical substances suspected of being harmful are:

- **Xenoestrogens** (DDT, DDE etc.)
- **Polychlorobiphenils**
- **Bisphenols** (PVC)
- **Phytoestrogens**
- **Heavy metals** (lead, mercury, cadmium, manganese, nickel, zinc, titanium, cobalt, argentum)
- **Drugs** (esp. those used for treating chronic pathologies)
- **Solvents**
- **Pesticides**

In fact, **female fertility** is also influenced by several daily behaviours and some food habits which have profoundly changed in the last 40 years due to the new role woman has taken on in our society.

Cigarette Smoke

The most dangerous mixture for the female reproductive function is smoke, followed by exposure to toxic substances and EDs.

The risk of infertility would be high for women who have been smoking 20 cigarettes/day since before the age of 18.

Cigarette Smoke

Cooper et al. 1995:

Basal FSH measurements (3rd day of the cycle) carried out in IVF candidate women:

- 66% higher in active smokers
- 39% higher in passive smokers

compared with non-smokers.

Post-clomiphene FSH levels in female smokers aged 35-39 are more than twice as high compared with female non-smokers.

Cigarette Smoke

Harmful effects on female fertility:

- ✓ steroidogenesis inhibition (especially estrogens)
- ✓ zona pellucida thickening
- ✓ increase in chromosomal abnormalities
- ✓ meaningful decrease in the follicular pool (studies carried out on rats) ⇒ early menopause

Cigarette Smoke

Smoke contains more than 4000 chemical compounds among which:

- 43 **carcinogens** and poisons
- more than 300 **polycyclic aromatic hydrocarbons**
- **nicotine and its metabolites**
- **cadmium**

Cigarette Smoke

Polycyclic Aromatic Hydrocarbons

Experimental studies carried out on rats proved that small doses of these compounds induced a considerable ↓ of the follicular pool.

Benzpyrene derivatives were found in theca and granulosa cells exposed to cigarette smoke

Cigarette Smoke

Nicotine and its metabolites

Both nicotine and other cigarette components produce direct inhibition of in-vitro follicular aromatase; this effect was considered the cause of the ↓ in the circulating ESTRADIOL levels which can be observed in female smokers undergoing ovarian stimulation.

Cigarette Smoke

Nicotine and its metabolites

Determine vasoconstriction, ↓ tissue oxygenation and concentrate in reproductive tissues.

Nicotine metabolites were found in the blood, urine, saliva and follicular fluid of both female smokers and women exposed to passive smoke.

Cigarette Smoke

Cadmium

- accumulates in the ovary and follicular fluid (study carried out on women undergoing IVF)
- causes an ↑ in oocyte and embryo chromosomal abnormalities
- causes the arrest of oocyte development in metaphase II.

Cigarette Smoke

Basically the data about the effect of smoke on fertility available are still few. However, several studies show:

- for the ovary: possibility that menopause will start about 2 years earlier \Rightarrow acceleration of the ageing processes for heart, skin, brain, blood vessels, urogenital apparatus
- for fertility: \downarrow conception rate, \downarrow successful ART cycles, \uparrow risk of miscarriage and fetal malformations, \uparrow risk of placental insufficiency, premature delivery and a delay in fetal growth due to direct toxicity on placental vessels.