Drug use in Pregnancy and Lactation

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Drug use in pregnancy

Drugs can be harmful for the unborn child

THE PLACENTA

Drugs pass placenta by passive diffusion

- lipid barrier between maternal and embryonic/fetal circulations
- slow process (used during caesarean section)
- non-ionized drugs pass more rapidly
- most drugs are small enough to pass
  exceptions: growth hormone, conjugated steroids
  …
- cuts peak concentrations in maternal plasma

Drug use in pregnancy

effects of toxic drugs

- malformation
- growth retardation
- fetal death
- functional defects in newborn
- premature birth

…..

Drugs should be used with caution during pregnancy

Drug use in pregnancy

Use of drugs in pregnancy is not always wrong

Some examples

- High fever is harmful for the fetus in the first months. Use of paracetamol is better then no treatment
- Diabetes during pregnancy needs intensive therapy with insulin
- Folic acid protects against spina bifida
- Anti-epileptics are teratogenic. But an epileptic insult may provoke harmful anoxia for the fetus.

Drug use in pregnancy

Before conception

Is damaged sperm teratogenic?

- Spermatozoa are continuously produced
- Damaged spermatozoa are slower and arrive late when the oocytes is already fertilized → mostly not harmful?
- May lead to infertility

→ paternal teratogenicity cannot fully be excluded.

advice: use of condoms when the man is taking products that are suspected to be harmful

termination of pregnancy because of paternal teratogenicity is not justified

Drug use in pregnancy

Before conception

Toxic chemicals and irradiation can damage

Oocytes

- all female germ cells develop prenatally. No germ cells are formed after birth
- Oocytes are in situ and not multiplying.
- teratogenic effects can become apparent after fertilization, maybe long after the presence of damage
- EMEA does not allow women with childbearing potential to take part in first in man studies

Drug use in pregnancy

The pre-implantation period (day 1 – day 7)

Damage of fertilized oocyte
→ death
→ complete recovery

Contact with toxic chemicals or irradiation does not increase the risk of fetal malformation

Drug use in pregnancy

The first trimester (day 8 – end of month 2)
Is the **most important period** for teratogenicity
Is period of formation of organs

3rd – 9th month
Less risk for malformations
except for urogenital tract
central nervous system
More functional effects
i.e. aminoglycosides nephro- & ototoxicity
salicylates increased risk of bleeding

Drug use in pregnancy

Delivery

drugs have effects in newborn

- avoid CNS depressants
  floppy infant syndrome
- avoid drugs with increased bleeding risk
  like anticoagulants, salicylates
  increased risk of cerebral hemorrhage during delivery
- NSAIDS and salicylates ↓ uterine contractility

Drug use in pregnancy

spontaneous malformations (=unknown origin)
2-4 %
Additional risk from drugs is small for most drugs

evidence for teratogenic effects

- golden standard is randomized controlled trial (RCT). ethical objections
- epidemiologic studies cannot establish proven causality
- large species differences in teratogenic effects

No drug is proven free from teratogenic effects

Drug use in pregnancy

Risk classifications

- Different risk classifications have been proposed.
- The FDA risk classification is widely used
- websites using FDA risk classification

www.safefetus.com

www.perinatology.com/exposures/druglist.htm

Risk classification of FDA

drug risks to the fetus runs from:

Category A (safest) →

Category X (known danger--do not use!)

Drug use in pregnancy

risk classification (FDA)

- **Category A**

  Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Drug use in pregnancy

risk classification (FDA)

- **Category B**

  Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women,

  or

  animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Drug use in pregnancy

risk classification (FDA)

- **Category C**
  Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women,
  or
  studies in women and animals are not available.

  Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Drug use in pregnancy

risk classification (FDA)

- **Category D**
  There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Drug use in pregnancy

risk classification (FDA)

- **Category X**
  Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both,
  and
  the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.

  The drug is contraindicated in women who are or may become pregnant.

Drug use in pregnancy

Very teratogenic drugs

- **Thalidomide (Softenon)**
  for treatment of leprosy, in oncology
  focomelia (short extremities)

- **Retinoids**
  multiple defects and malformations
  adequate birth control needed after
  isotretinoin for 1 month
  acitretin/etretinate for 2 years

- **Cytostatics**

Drug use in pregnancy

Late appearance of teratogenicity
example: DES (diethylstilboestrol)

adenocarcinoma of vagina during adolescence
in daughters
is the only proven example in human beings of prenatally-caused cancer

other: genital malformations in newborn (25%)
if DES was given in first trimester

Drug use in pregnancy

Teratogenicity versus harm from disease
example: Antiepileptics

- harm from: epileptic insult ↔ drugs

advice

- inform patient that chance of malformation increases 2-3 fold (is still ≤ 10%)
- evaluation of treatment before pregnancy. Can treatment decreased or stopped?
- Valproic acid should be changed to another anti-epileptic (very teratogenic [±15%] many malformations like neural tube, spina bifida)
- offer prenatal diagnosis?!

Drug use in pregnancy

Some examples

- **ACE-inhibitors**
  malformations (oligohydramnion)
- **Tetracyclins**
  caries, tooth coloration
- **Coumarins**
  bone malformation
  bleeding risk

Drug use in pregnancy

Frequently used teratogenic agents

- **Alcohol**
  craniofacial skeletal abnormalities
  growth retardation
  mental disorders

- **Smoking**
  orofacial clefts 1/500 – 1/183
  lower birth weight
  premature birth

Drug use in pregnancy

Frequently used teratogenic agents

- **Coffee**
  > 300 mg caffein/day (>3-6 cups of coffee)
  ↑ risk of fetal death
  advice: limit coffee to 3 cups/day

- **Vitamin A**
  teratogenic in animal model, in human beings?
  avoid > 3 mg = 10.000 IE
  liver contains large amounts of vitamin A

Drug use in pregnancy

Herbs not recommended or contraindicated

- herbs that stimulate menstruation
  i.e. nettle root
- alkaloid-containing herbs
  coffee, mandrake (podophyllin) …
- essential oils
  rosemary …
- anthraquinone laxatives
  senna …
- herbs with potential hormonal action
  hops, ginseng, licorice …

Drug use in lactation

Toxic effect of drug depends on:

- free concentration of drug in maternal plasma
  transfer from plasma to milk
    passive diffusion
    non-ionized drugs pass more rapidly
    lipophilicity
- amount ingested by the newborn
    concentration in milk
    milk volume
- kinetics in newborn
    immature liver and renal function

→ **hard to predict**

Drug use in lactation

advice

- use the lowest possible dose
- close observation of child
- time of drug intake versus breast feeding?
- avoid drugs like
    - aminoglycosides
    - thyrostatics
    - chloramphenicol
    - tetracyclins
    - immunosuppressants
    - cytostatics

Drug use in pregnancy and lactation

conclusions

pregnancy

- some drugs have proven teratogenicity
- no drug is proven free of teratogenicity
- For some drugs there is enough evidence for a low risk of teratogenicity

lactation

- the amount of drug ingested by breastfeeding is difficult to assess
- careful observation of the baby is advised
- some drugs are absolutely contraindicated