Postmarketing teratology surveillance in Hungary: a successful model

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Arguments for the postmarketing surveillance of drug teratogenicity

- Drugs are not tested in pregnant women before they are released on the market.
- More than 90% of pregnant women use medicinal products (70% of pregnant women used drugs) in Hungary.
- A better balance is needed at the evaluation of risk and benefit of drug use.

The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) was established in 1980

The objective of the **surveillance of CAs** is to evaluate the study population at large for the determination of changes in the baseline occurrences of CAs and to detect their causes

CA-monitoring means to study a population at risk (i.e., exposed to known or suspected environmental factors such as teratogens and/or mutagens)

Study groups of the HCCSCA

1. **Cases** affected with CA from the HCAR except three mild CAs and CA-syndromes with known origin (except Down syndrome)
2. **Patient controls** affected with Down syndrome from the HCAR
3. **Population controls:** newborn infants without CA from the National Birth Registry of the Central Statistical Office

Matching:

– sex

– birth week

– district of parents' residence

Two population controls for each case

Data collection in the HCCSCA

1. Antenatal care logbook and available medical records (discharge summary): prospective data in the three study samples
2. A post-paid structured questionnaire (+memory aid = list of drugs and diseases + suggestion to invoke expert's help): retrospective data in the three study samples
3. Regional district nurses visit and question non-respondent families in the case and patient control samples and in a small sample of population controls

Missions of the HCCSCA

1. Postmarketing surveillance of medicine teratogenicity.
2. To obtain informed consent for further registration in the HCAR and investigation of cases.
3. To have appropriate exposure data.
4. To improve the validity of CA diagnosis.
5. To expand the data set of the HCAR including confounders.
6. To inform parents about the possible causes, treatment and rehabilitation choices for their child's CA, in addition prevention in next pregnancies.
7. To provide case-control data for scientific studies.

The data set of the HCCSCA

Study groups	1980-1996	1997-2003	Total
Cases	22,843	7,079	29,922
Population controls	38,151	14,448	52,599
Patient controls	834	233	1,067

Principles of the HCCSCA

- Differentiation of
  - isolated CAs (some teratogenic factors trigger genetic liability in CAs of multifactorial origin)
  - multiple CAs (true teratogens cause multiple CAs)
- Noxa specificity: different CA entities and medicines are evaluated separately
- Time factor: in general second and third gestational months are evaluated as a critical period of most major CAs
- Recall bias is limited due to the use of medically recorded prospective exposure data and due to the comparison with patient controls

Principles of teratogenic evaluation of medicines

- Different medicines within the same group (as penicillins or tetracyclines) cannot be combined due to their different

  – chemical structure

  – indications (i.e., underlying diseases) and

  – route of administration (oral, parenteral , etc.)

The occurrence of two oral tetracyclines intakes during pregnancy

Tetracyclines	Cases (N=22,843)		Population controls (N=38,151)		OR	95% CI
	No.	%	No.	%		
Oxytetracycline	216	0.94	214	0.56	**1.7**	**1.4, 2.0**
Doxycycline	75	0.33	98	0.26	1.3	0.8, 2.1

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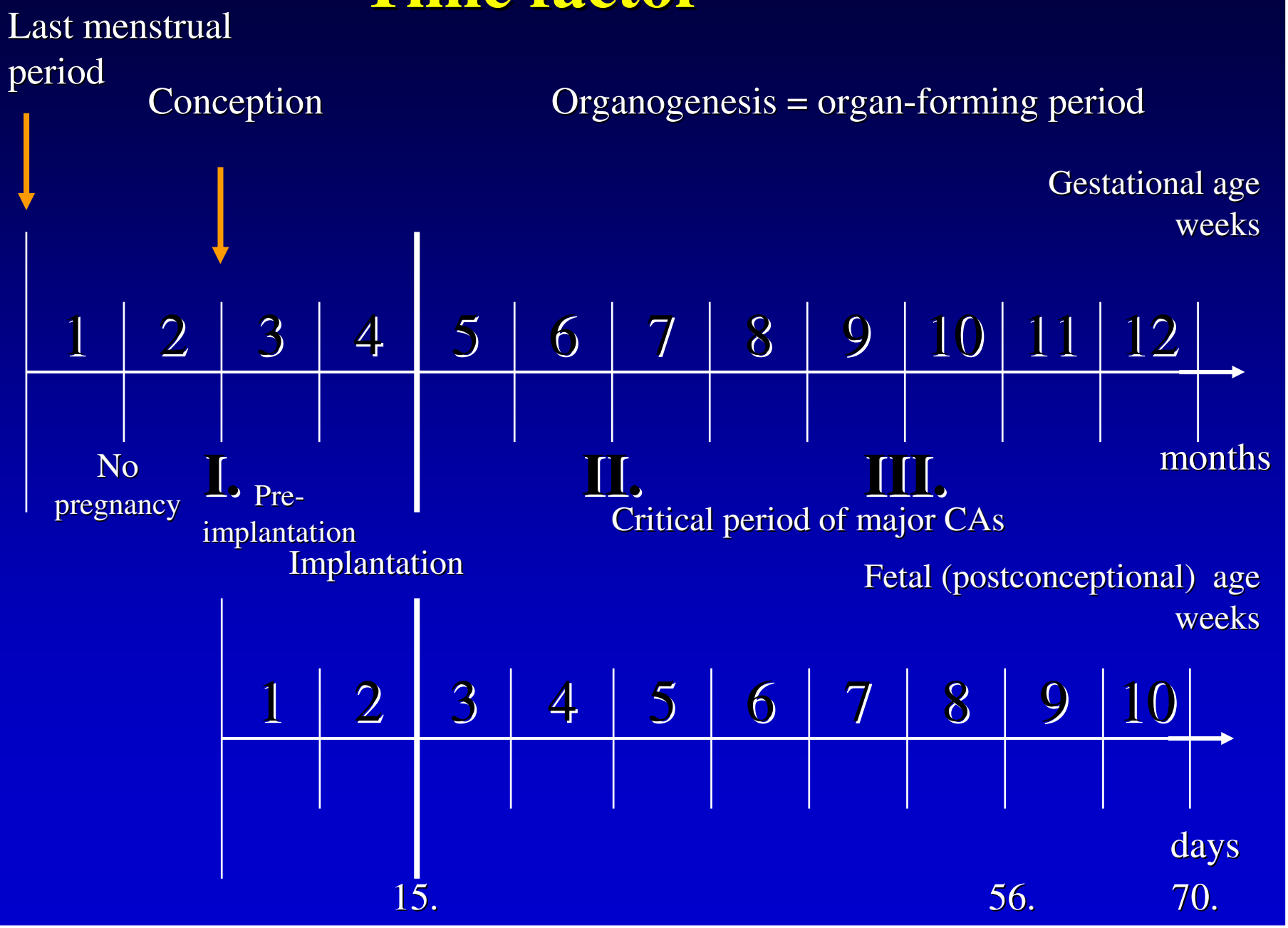
Time factor


Last menstrual period
Conception
Organogenesis = organ-forming period
Gestational age weeks
1 2 3 4 5 6 7 8 9 10 11 12
months
No pregnancy
I.
Pre-implantation
II.
III.
Critical period of major CAs
Implantation
Fetal (postconceptional) age weeks
1 2 3 4 5 6 7 8 9 10
days
15.
56.
70.

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Recall bias

Cases

The birth of an infant with CA is a serious traumatic event for mothers who therefore try to find a causal explanation

Controls

After the birth of a healthy baby the mother is happy and she forgets the events during pregnancy

This bias mimics increased (i.e. overestimated) teratogenic risk up to a factor of 1.9.

How we can reveal and limit recall bias

1. “Time factor”: we evaluate the effect of teratogenic agents only during the critical period for specific CAs (because we expect an underreporting of exposure in both the critical and non-critical periods of CAs in the control group).
2. “Reference standard”: the use of more valid source of exposure data, e.g. prospective medically recorded data.
3. “Patient controls”: cases with Down syndrome have a similar degree of recall bias.

At present the teratogenic risk of drugs is exaggerated.

Possible causes:

1. Positive results of animal investigations are extrapolated for the human fetus.
2. Poor quality of human studies (e.g. recall bias is neglected).
3. Publication bias: editors prefer to publish “positive” findings.
4. Self-defensive attitude of medical doctors.
5. Defensive policy of pharmaceutical companies.
6. Classification policy of drug regulatory agencies.
7. Potential parents wish to have a “100%” healthy baby.

The main hazards of exaggerated teratogenic risk of drugs

1. Several pregnant women are not treated with the effective and necessary drugs.
2. Many planned and/or wanted pregnancies are terminated.
3. Pregnant women have a permanent psychological stress due to the necessary drug treatment.

Final conclusion

- A better balance is needed at the evaluation of risk and benefit of drug use during pregnancy.
- The exaggerated teratogenic risk of drugs is much more harmful for the fetus than the true teratogenic effect of some drugs themselves.
- Experts, particularly medical doctors, need a better education regarding human teratology.