Rational for birth defect registry, surveillance and monitoring based on the Hungarian experiences

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Epidemiology

Descriptive

a) Prevalence/incidence

b) Characteristics of pathological conditions
- time/space distribution
- sex ratio
- age, etc.

Analytical

Case-control
Cohort, etc.

Disaster

Natural and human-made

Ad hoc studies

Public health systems
- registries
- surveillances
- monitorings

I.

Registry of birth defects

A registry is a file of documents containing uniform medical and/or socio-demographic information about individual persons, collected in a systematic and comprehensive way in order to serve a pre-determined purpose.

The Hungarian Congenital Abnormality Registry (HCAR)

was established in 1962 and Dr. Czeizel was director of the HCAR between 1970 and 1998.

The task of the HCAR is the registration of *cases* with congenital abnormalities (CAs) = structural birth defects.

Missions of the HCAR

1. To determine recorded rates of Cas.
2. To detect temporal and/or spatial increases.
3. To help plan medical and social services for affected persons.
4. To estimate the public health importance of different CAs so that resources can be properly allocated.

Main characteristics of the HCAR

- **Study population:** terminated fetuses from the second trimester of gestation through still- and live births till the age of one year.
- **Notification:** compulsory for medical doctors.
- **Source of information:**
  1. Fetal diagnostic centers
  2. Obstetrical institutions
  3. In- and outpatient pediatric clinics
  4. Pathological institutions
  5. Others
- **Unit:** informative affective offspring (cases) with isolated and multiple abnormalities.
- **Ethics:** written informed consent.

Classification of CAs (I)

Lethal: stillbirth, infant death or elective termination of pregnancy in more than 50% of cases (e.g. anencephalus)

Severe: death and/or severe handicap without medical intervention (e.g. omphalocele)

together **major** CAs

Mild: needs medical intervention but life expectancy is good (e.g. undescended testis)

- - -

Minor anomaly (morphologic variant): no serious medical or cosmetic consequences (e.g. simian crease or umbilical hernia)

Major findings of the HCAR, 1970-1998

- Annual total (fetal + birth) prevalence of cases with CAs was 35 per 1000 total births.
- Approximately 90% of major CAs were reported to the HCAR.
- Minor anomalies were recorded but excluded from calculation of rates of different CAs.

Criteria of good registries

Good validity of CA-diagnosis

Completeness of ascertainment

Pathogenetically oriented classification

Validity of diagnosis in common CAs

Common CAs	Proportion (%) of misdiagnoses
Cleft lip ± palate	0
Neural-tube defects	3
Congenital hypertrophic pyloric stenosis	4
Down syndrome	5
Hypospadias	6
Undescended testis	9
Ventricular septal defect	10
Talipes equinovarus	12
Congenital dysplasia of hip	16
Congenital inguinal hernia	17

Validity of diagnosis in isolated congenital limb deficiencies (CLD) as a bad example

Types of CLD	Reported prevalence per 1000	True prevalence per 1000
Amputation		
Terminal transverse	0.01	0.12
Amniogenic	0.02	0.09
Longitudinal		
Radial-tibial	0.01	0.03
Ulnar-fibular	0.02	0.07
Split hand + foot	0.02	0.03
Intercalary		
Phocomelia	0.10	0.01
Femoral head aplasia	0.00	0.01
Total	0.18	0.36

Completeness of ascertainment in common CAs

Category/type of common CAs	Completeness of notification (%)
Isolated	
Neural-tube defects	87
Ventricular septal defect	64
Cleft lip ± palate	98
Congenital hypertrophic pyloric stenosis	94
Undescended testis	31
Hypospadias	83
Congenital dysplasia of hip	63
Talipes equinovarus	95
Congenital inguinal hernia	30
Multiple	
Down syndrome	73

Pathogenetically oriented classification of CAs (II)

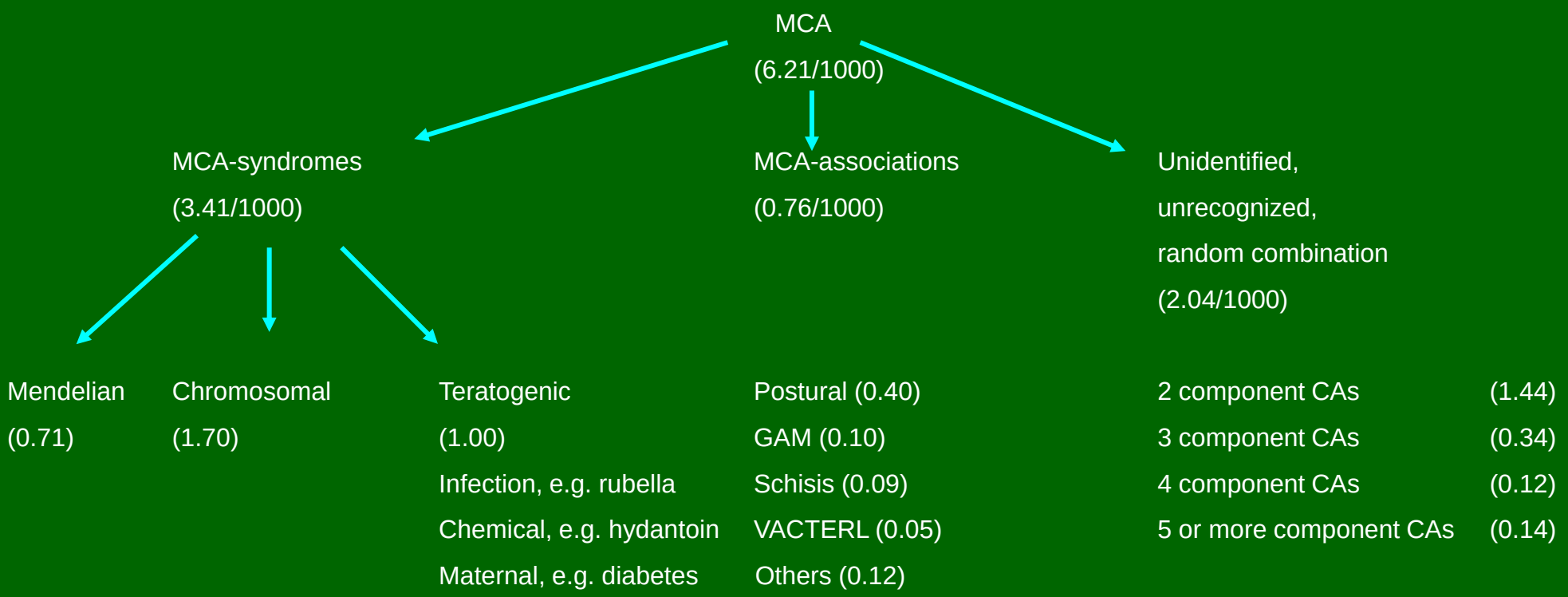
Isolated CAs: only one organ system is affected

1. single (e.g. ventricular septal defect)
2. complex (e.g. Tetralogy of Fallot)
3. polytopic field defect (e.g. holoprosencephaly)
4. sequence (e.g. spina bifida with hydrocephalus and clubfoot)

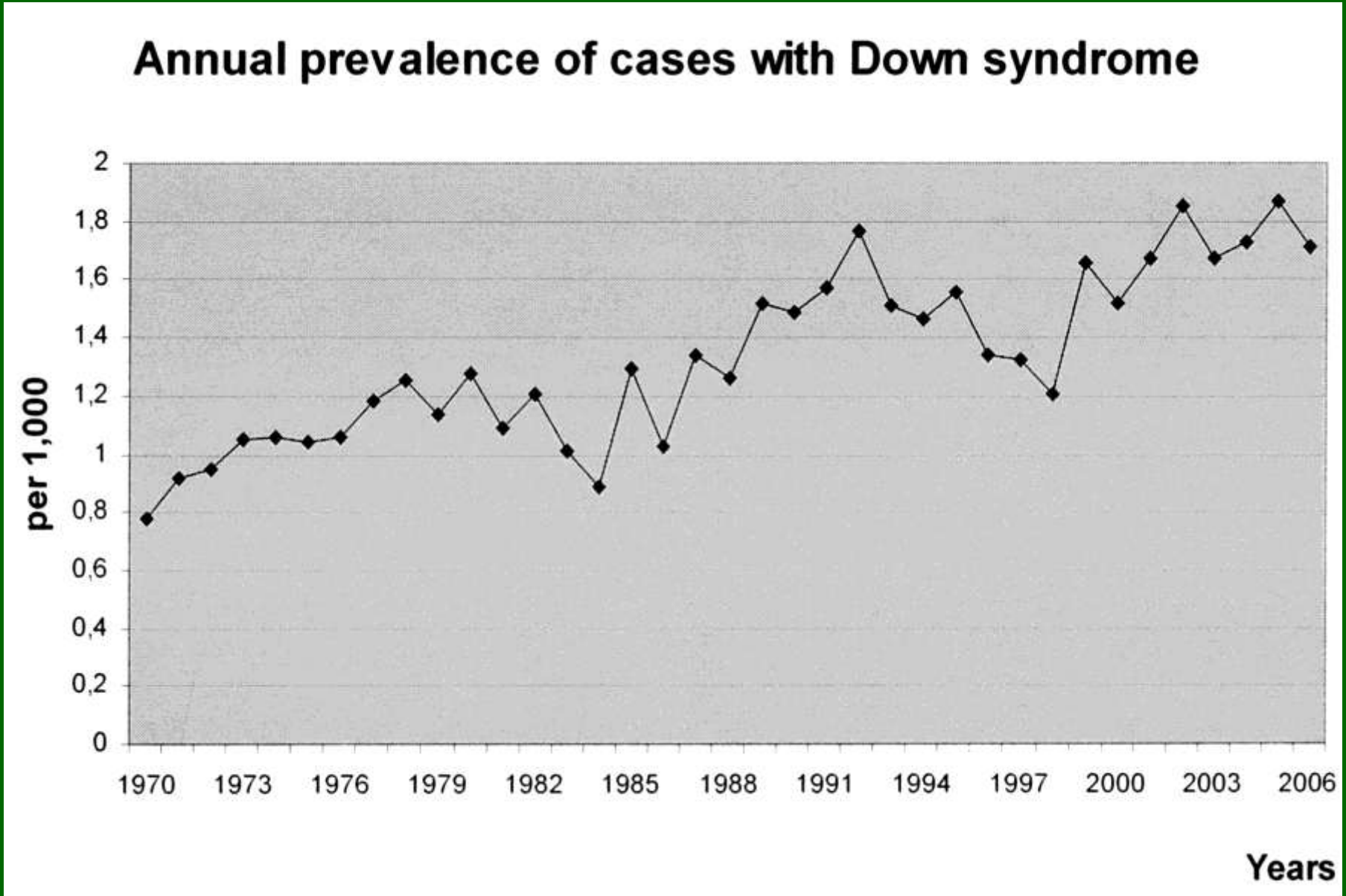
Multiple CA (MCA): concurrence of 2 or more CAs in the same person affecting at least 2 different organ systems

1. MCA-syndromes (e.g. Down-syndrome)
2. MCA-associations (e.g. VACTERL)
3. Random combination
4. Unclassified (unidentified, unrecognized, random combination together)

Classification of MCA groups and their total (birth+fetal) prevalence per 1,000 births in the HCAR, 1973-1982



Mission 1


Annual prevalence of cases with Down syndrome
per 1,000
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
1970
1973
1976
1979
1982
1985
1988
1991
1994
1997
2000
2003
2006
Years

Mission 2/a

Temporal cluster of congenital limb deficiencies

Year	No.	Rate per 1,000
1971	45	0.30
1972	40	0.26
1973	52	0.33
1974	63	0.34
1975	**91**	**0.46**
1976	**83**	**0.45**
1977	**115**	**0.64**
1978	**103**	**0.61**
1979	57	0.36
1980	44	0.29

Mission 2/a

Case-control study of congenital limb deficiencies

Congenital limb deficiencies	Cases			Matched controls			Attributable risk (%)
	N.	Estrogen		N.	Estrogen		
		No.	%		No.	%	RR (with 95%)
Total	274	8	2.9	274	2	0.7	4.1 (0.0-10.2) 3.1
Unimelic	138	6	4.3	138	1	0.7	6.1 (0.0-18.6) 5.1
Terminal transverse	63	4	6.3	63	0	0.0	9.0 8.0

High dose of abortifacient estrogens caused this cluster

Mission 2/b

Spatial cluster of CAs

Of 15 live births in one Hungarian village in 1989-1990, 11 (73%) were affected by CAs and 6 were twins.

Of 11 cases, 4 had Down syndrome (this number was 223 times greater than that in the Hungarian population).

A case-control study indicated the excessive use of trichlorfon in local fish farms. The content of this chemical was very high in fish (100 mg/kg) and ten pregnant women (including all mothers of babies with Down syndrome) had consumed contaminated fish in the critical period for CAs observed.

Mission 3

To help plan medical and social services for affected persons

Medical services

congenital cardiovascular abnormalities
estimated livebirth prevalence: 0.1/1000
true livebirth prevalence: 10.4/1000

Social service

Down syndrome: inverse association between incidence and prevalence

Mission 4

Public health importance of 10 common CAs in Hungary

Common CA	Total years lost	Total years of actually impaired life	Total prevalence per 1000
Neural-tube defects	621	189	2.8
Down syndrome	283	636	1.3
Ventricular septal defect	92	0	2.0
Cleft lip ± palate	22	141	1.0
Congenital inguinal hernia	4	0	11
Undescended testis	0	980	3.6
Hypospadias	0	308	2.2
Congenital dysplasia of hip	0	180	13.6
Talipes equinovarus	0	101	1.5
Congenital hypertrophic pyloric stenosis	0	0	1.5

Conclusions

HCAR was the first national-based CA-registry in the world.

HCAR had the highest recorded total prevalence of cases with CA in the world (4.8% in 1984).

HCAR was able to fulfil its planned missions.

Recommendation

The establishment of CA registries is the first public health task to determine the total (birth + fetal) prevalence of CA and to describe their characteristics (e.g. sex) in the study population.

Weakness: in general CA registries are not able to detect the causes of Cas.

II.

Case-Control Surveillance of Congenital Abnormalities

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.

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.

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 in the year when cases were born

– 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 two samples of population controls.

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) and of multiple CAs (true teratogens cause multiple CAs).
- Teratogen 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.
- The effect of confounders.
- Recall bias is limited due to the use of medically recorded prospective exposure data and due to the comparison with patient controls.

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.

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),

  – 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

Conclusion

Oxytetracycline indicates teratogenic risk

while

Doxycycline did not show teratogenic risk

within the group of tetracyclines

The evaluation of teratogenic potential of medicinal products

1. About 2% of all CAs may be associated with the use of the so-called human teratogenic drugs.

2. Sometimes drugs can prevent the teratogenic potential of maternal diseases (e.g. antifever drugs in influenza with high fever).

3. Folic acid and/or folic acid containing multivitamins can prevent some CAs.

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.

Conclusions

- 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.

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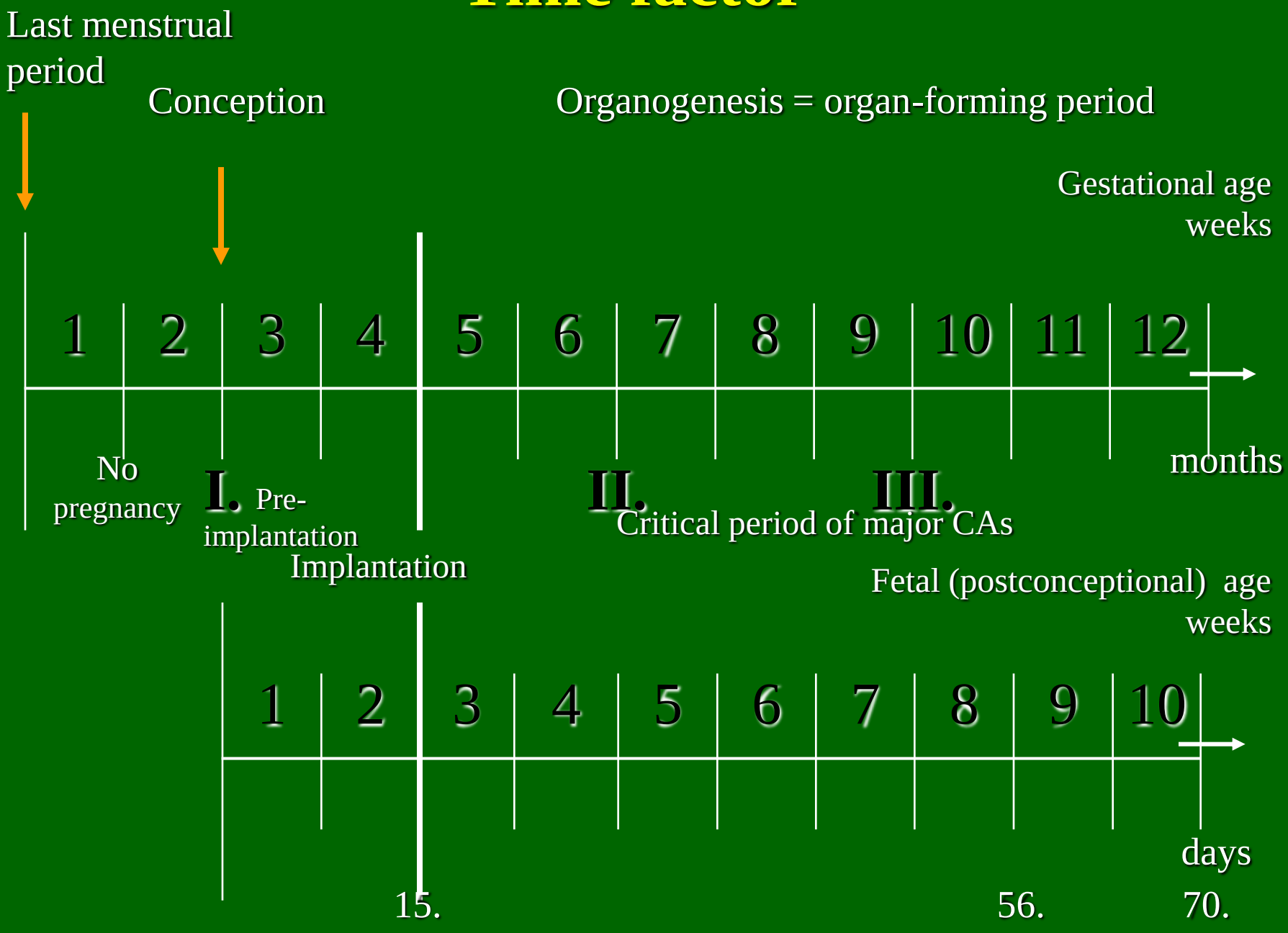
Time factor


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.

Conclusion: The first trimester concept is unscientific

1. Gestational age is calculated from the first day of the last menstrual period, thus pregnant women are not pregnant in the first two weeks of pregnancy. Zygotes in the third and blastocysts in the fourth week contain stem cells and teratogenic agent cannot induce CA in stem cells. Thus first gestational month is out of critical period of CA.

2. Some CAs (e.g. hypospadias, cleft palate) had critical period after the third gestational month.

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Confounder factors of the HCCSCA

Sociodemographic factors (confounders)

- maternal age
- birth order (parity)
- socioeconomic status etc.

Pregnancy complications

- *nausea and vomiting in pregnancy*
- threatened abortion/preterm delivery
- gestational diabetes etc.

Maternal factors

- acute diseases
- chronic diseases
- occupational exposures etc.

Medicine intakes

- drugs
- pregnancy supplements

Family history

- CA
- consanguinity

Association between nausea and vomiting in pregnancy (NVP) and risk for CAs

Degree of NVP	Case mothers (N=22,843) No.	%	Control mothers (N=38,151) No.	%	Comparison OR	95% CI
Mild	10,721	46.9	19,192	50.3	0.91	0.88-0.94
Severe	1,746	7.6	3,869	10.1	0.74	0.70-0.78
Very severe	33	0.1	92	0.2	0.58	0.39-0.86

CA groups which had a significantly lower total prevalence after NVP

Category/type CAs	OR	95% CI
Isolated		
Neural-tube defects	0.50	0.37-0.70
Cleft lip ± palate	0.53	0.32-0.89
Renal a/dysgenesis	0.23	0.06-0.96
Obstructive CAs of urinary tract	0.32	0.18-0.58
Cardiovascular CAs	0.68	0.57-0.81
Multiple CA	0.74	0.68-0.79

Hypothesis for the CA protective effect of NVP

Some foods are toxic

Strong placenta

Helicobacter pylori

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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.

Benefits of the HCCSCA

1. Large population-based case-control data set in racially homogeneous Hungarian people.
2. Matching of cases and population controls.
3. Patient controls.
4. Prospective medically recorded data.
5. It is possible to organize follow-up study.

Conclusions

concerning the missions of the HCCSCA

1. Postmarketing surveillance of medicine teratogenicity is feasible.
2. Informed consent was provided by 98% of cases and patient controls.
3. Exposure data are appropriate (prospective, medically recorded, exposure time is known).
4. The validity of CA diagnosis was improved significantly.
5. The data set of the HCAR was expanded to include potential confounders.
6. Parents of cases were informed about their child's CA (this activity improved the compliance of parents).
7. The data set has been used in scientific studies.

III.

Monitoring of CAs

to study/evaluate populations at risk

An Example is given in the presentation of Professor Czeizel
self-poisoning during pregnancy