Evaluation of observational data in human teratogenicity studies of the Berlin Embryotox project

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Berlin Embryotox

Tasks

- Risk information to HCP and pregnant women
- Pharmacovigilance pregnancy
  on behalf of Federal Institute for Drugs and Medical Devices
- Research

Multidisciplinary team,

i.e. obstetrics/gynaecology, paediatrics, human genetics, internal medicine, anaesthesiology, pharmacy, biometrics

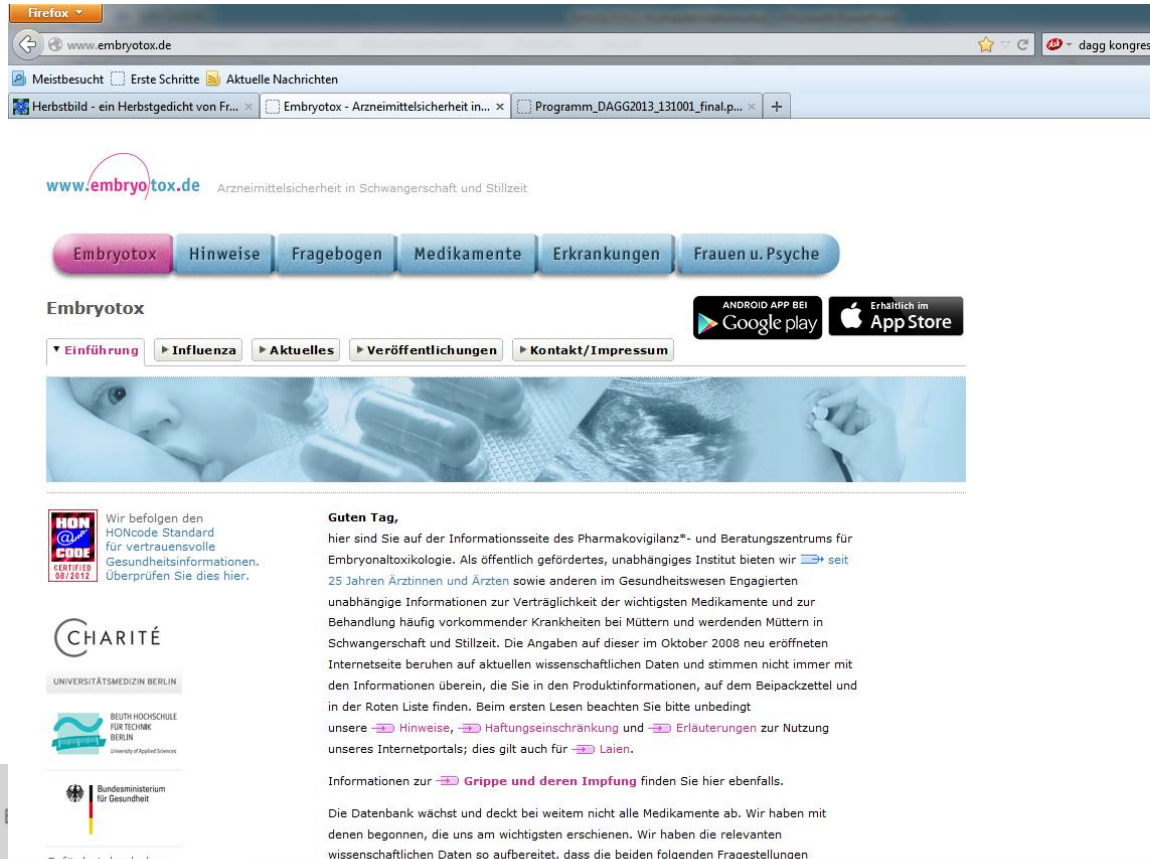
To improve mother-child health

- Prevention of birth defects
- Avoidance of non-prescription or non-compliance
- Prevention of terminations of pregnancies

} due to overestimated drug risks

Embryotox drug risk information via

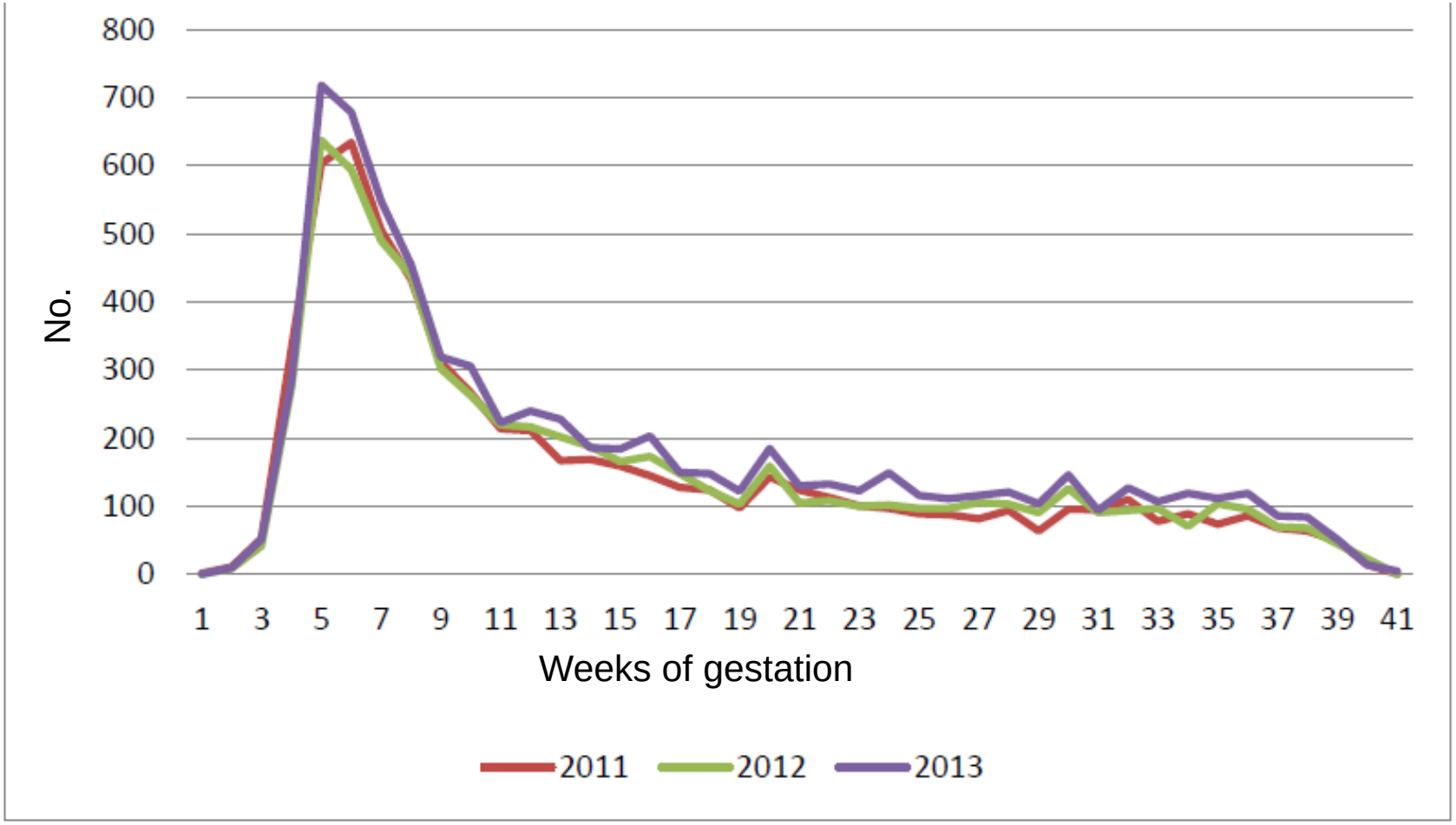
- Open access information database www.embryotox.de (~1 200 000 visitors/year or ~4 000/d)



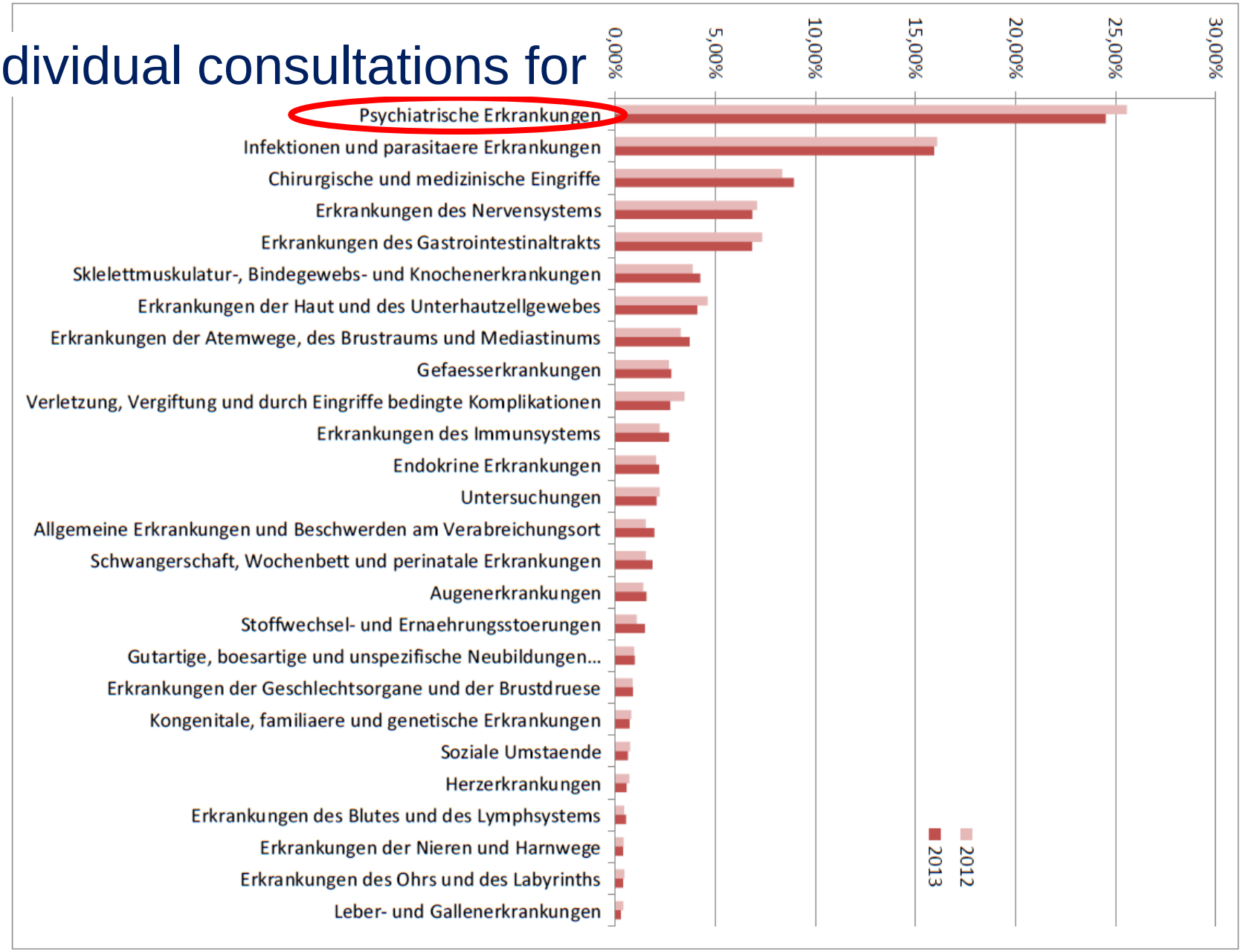
Embryotox drug risk information via

- Open access information database www.embryotox.de (~ 1 200 000 visitors/year or 4 000/d)
- Individual consultation via phone, email, online questionnaire or letter (~14 000 consultations/year or ~70/d)
  ⟹ followed by structured protocol of pregnancy outcome

Consultations - gestational week at 1st contact



Individual consultations for



Sources of information re. drug effects in (human) pregnancy?

Observational data, evaluated

- case by case
- cohort studies (e.g. Embryotox patient database)
- case-control-studies (e.g. birth defect registries)
- prescription studies

Embryotox-patient database

- ~50 000 exposed pregnancies with complete follow-up
- ~4 000 annual increment

Maternal data:

Age, education, (obstetric) history, family history
Gestational week at 1st contact
Drugs incl. hormones, social drugs, X-ray, fever, weight loss
Fertility problems etc.

Follow-up:

Course of pregnancy (and of chronic diseases)

Prenatal diagnostics

Pregnancy outcome:

Gestational week and fetopathology if miscarriage
Status of newborn until week 5

Embryotox - cohort studies: comparison groups

- Disease-comparison group: Similar disease but no medication or other than study group
- Comparison group II: no teratogens and fetotoxicants:

  Acitretin
  Isotretinoin
  MTX
  Mycophenolate
  Thalidomide
  Valproic acid
  Angiotensin-II receptor blockers (sartanes) (only when used in 2nd or 3rd trimester)
  ACE inhibitors (only when used in 2nd or 3rd trimester)

  Excluded treatment indication:
  Malignancies (MedDRA code: Malignant or unspecified tumors (SMQ 20000091), ICD-10: C00-D09)
  Malignancy related conditions (MedDRA: SMQ 20000092), ICD-10: C00-D09)

2nd generation antipsychotics

(Habermann et al. J Clin Psychopharmacol 2013)

Publication selected for Mitchell B. Balter Award 2013

- In spite of frequent use in pregnancy insufficient experience

  [Reis & Källén. J Clin Psychopharmacol. 2008; McKenna et al. J Clin Psychiatry. 2005]

2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)

	SGA	FGA	Controls
Pregnancies	561	284	1122
Exposure at least during 1st trimester	513	256	
Exposure at least until delivery	235	99	

2nd generation antipsychotics

(Habermann et al. J Clin Psychopharmacol 2013)

SGA	
Olanzapine	**187**
Quetiapine	**185**
Clozapine	**73**
Risperidone	**64**
Aripiprazole	**60**
Ziprasidone	37
Amisulpride	16
Zotepine	2

FGA			
Haloperidol	129	Pipamperone	14
Promethazine	101	Fluspirilene	8
Flupentixol	66	Zuclopenthixol	8
Chlorprothixene	37	Prothipendyl	7
Melperone	29	Thioridazine	6
Sulpiride	29	Triflupromazine	6
Fluphenazine	20	Perphenazine	5
Levomepromazine	18	Pimozide	5
Perazine	16	Clopenthixol	1

2nd generation antipsychotics

(Habermann et al. J Clin Psychopharmacol 2013)

		SGA	FGA	Controls
Miscarriages cumulative incidence		**24%**	**16%**	**20%**
	95% CI	14% - 39%	10% - 26%	15% - 26%
	n	568	289	1146
ETOP cumulative incidence		**17%**	**21%**	**3%**
	95% CI	13% - 23%	14% - 31%	2% - 5%
	n	568	289	1146
Preterm children gestation wk < 37		**9.1%**	**15.1%**	**8.7%**
	95% CI	6.5% - 12.1%	10.8% - 20.3%	7.0% - 10.6%
	n	453	238	1014
Birth weight term births	median	**3400 g**	**3380 g**	**3440 g**
	25Q/75Q	3080 - 3750	2959 - 3710	3160 - 3751
	n	398	190	922

2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)

Major birth defects:

		OR	CI (95%)
SGA vs. FGA	adj.	**1.27**	**0.57 – 2.82**
(430/213)	crude	1.22	0.55 – 2.70
SGA vs. Controls	adj.	**2.17**	**1.20 – 3.91**
(430/1014)	crude	2.13	1.20 – 3.83
FGA vs. Controls	adj.	**1.71**	**0.78 – 3.79**
(213/1014)	crude	1.75	0.80 – 3.80

2nd generation antipsychotics

(Habermann et al. J Clin Psychopharmacol 2013)

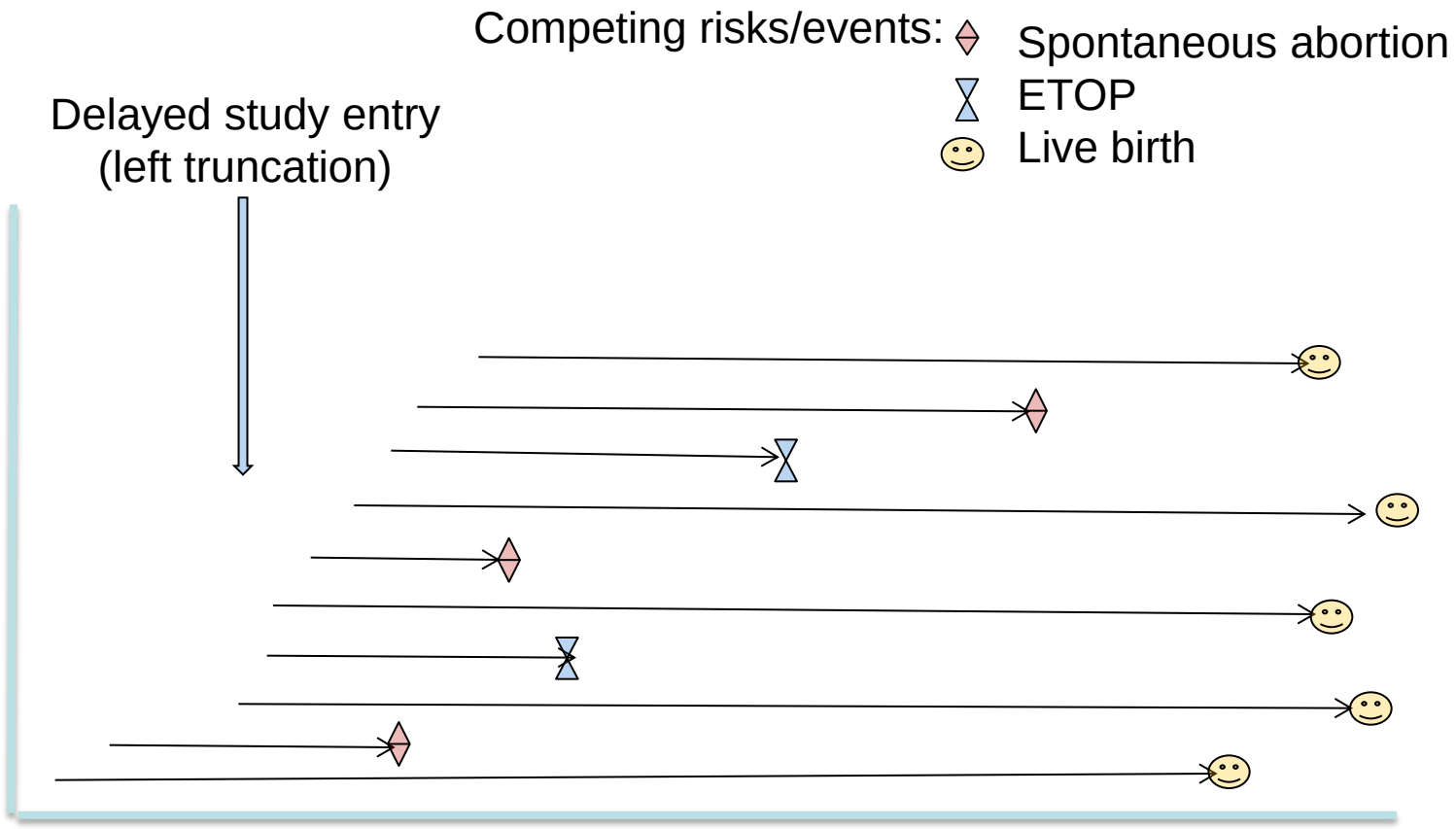
	SGA	FGA	Controls
Neonatal adverse effects	**15.6%** (37/237)	**21.6%** (22/102)	**4.2%** (43/1014)

Embryotox – methods, e.g. Cumulative incidences of pregnancy outcomes

To be considered:

- delayed study entry, depends on recognition of being pregnant and contact to the study center (Embryotox)
- Abortion and ETOP are “competing” events

Methods: Cumulative incidences of pregnancy outcomes



Weeks of gestation	5	6	7	8	9	10	11	12	20	30	40
Pregnancies at risk	1	2	5	8	8	7	6	6	5	4	1

Methods: Cumulative incidences of pregnancy outcomes

Crude rates for different causes of end of pregnancy

	Exposed	Control
Live birth	0.53	0.91
Induced abortion	0.22	0.02
Spontaneous abortion	0.25	0.07

Meister et al. Reprod Toxicol 2008

Methods: Cumulative incidences of pregnancy outcomes

Crude rates for different causes of end of pregnancy

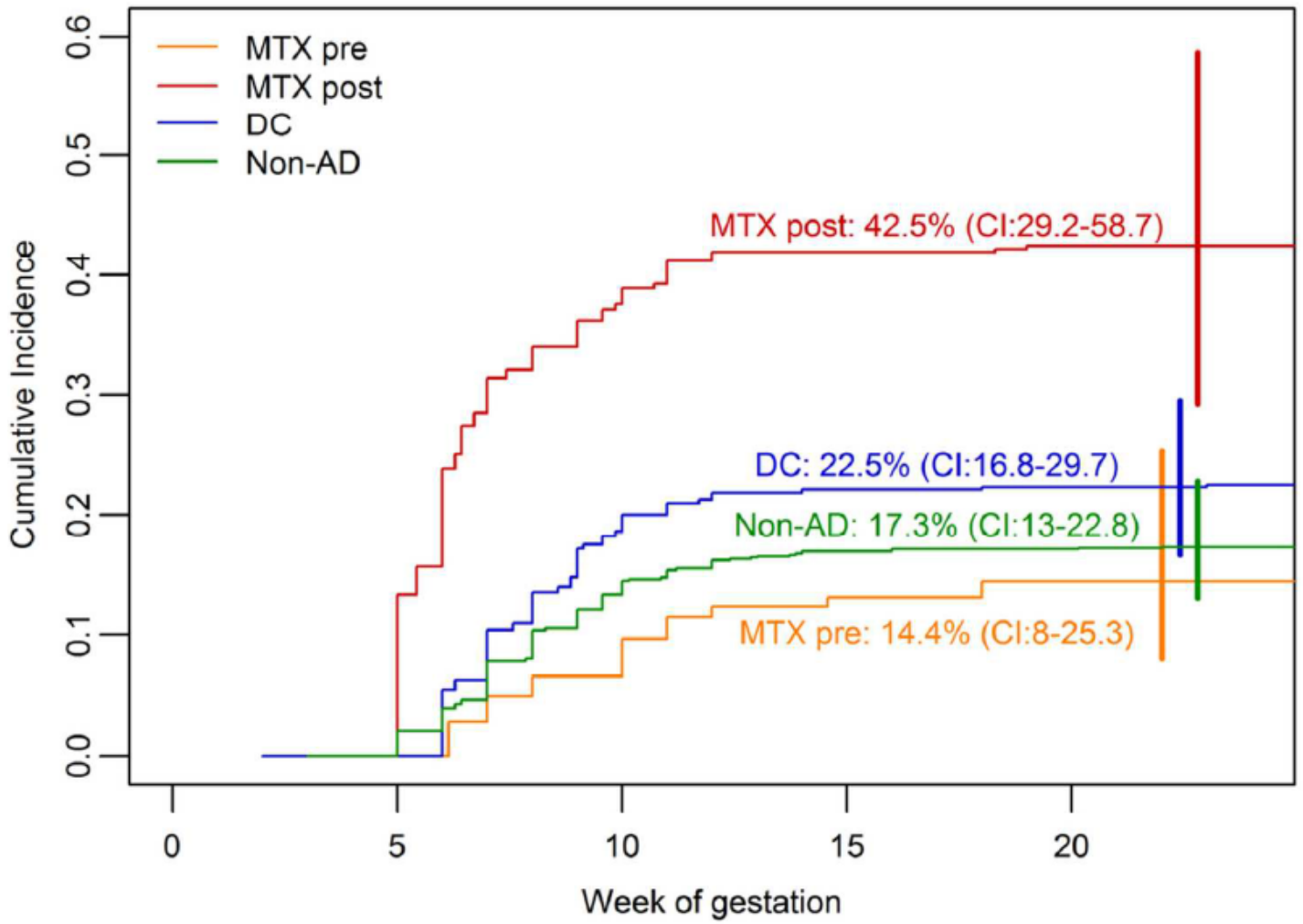
	Exposed	Control
Live birth	0.53	0.91
Induced abortion	0.22	0.02
Spontaneous abortion	0.25	0.07

Causes for end of pregnancy by exposure, estimates of cumulative incidences, adapted for delayed entry

	Exposed		Control	
	$\hat{p}$	SE	$\hat{p}$	SE
Live birth	0.35	0.01	0.80	0.001
Induced abortion	0.29	0.04	0.04	0.01
Spontaneous abortion	0.36	0.05	0.16	0.02

Meister et al. Reprod Toxicol 2008

Low dose MTX: Cumulative incidences for abortions



Weber-Schoendorfer et al. Rheumatologic MTX. Arthritis Rheumatol 2014

Exposure time based risk analysis II - Fluoroquinolones

Tabelle 3.16 Fehlbildungsrisiken nach Expositionszeit (Odds Ratios und Konfidenzintervalle).

Expositions-beginn (SSW)	Gesamte Fehlbildungen		Große Fehlbildungen	
	Odds Ratio	KI (95%)	Odds Ratio	KI (95%)
2+0 bis 2+6	0,92	0,49–1,72	0,4	0,10–1,64
3+0 bis 3+6	1,09	0,61–1,96	1,20	0,52–2,78
4+0 bis 4+6	0,70	0,32–1,52	0,74	0,23–2,36
5+0 bis 5+6	0,54	0,20–1,47	0,98	0,31–3,16
6+0 bis 6+6	0,78	0,24–2,53	1,26	0,30–5,27
7+0 bis 7+6	1,81	0,64–5,18	2,10	0,50–8,89
Ab 8+0	0,44	0,06–3,24	–	–

KI: Konfidenzintervall; SSW: Schwangerschaftswoche.

Padberg, Dissertation 2014

Exposure time based risk analysis III -Coumarins

sent a major teratogenic risk in early pregnancy. Similar to published case reports, there is no indication of coumarin embryopathy in our large cohort of those live births (n=235) exclusively exposed ≤ week 8 (see Table 3). There seems to be a stronger risk for (major) birth defects when exposure has taken place (exclusively) after week 8 (OR 10.53; 95% CI 2.47–44.93). However, this OR should be carefully interpreted because there were only a few cases in this group (n=23). The rate of major birth defects

Schaefer et al. Pregnancy outcome Vitamin K antagonists. Thromb Haemost 2006

Limitations of Embryotox patient database

- Selected population may not be representative for all pregnant women under index treatment/exposure:
  - Self selection by HCP or patient
  - Better education and pregnancy care, i.e. at lower risk
- Paediatric reports of heterogeneous quality
- Exposed cohorts too small to investigate associations with specific rare birth defects

Advantages of Embryotox patient database

- Pre-existing infrastructure (for consultation)
- High quality real-time ascertainment of exposure data
- Motivated “respondents”, only 20% non-responders
- Spontaneous abortions and ETOPs included
- Fetopathology included
- Plausibility control and call backs to involved HCP
- Comparison cohorts

Pharmacology / Clinical Medicine / Toxicology

Third Edition

Drugs During Pregnancy and Lactation

Treatment Options and Risk Assessment

Edited by

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