Time matters – Die Rolle der Expositionszeit bei der Beurteilung des Risikos von Arzneimitteltherapien in der Schwangerschaft

Reinhard Meister

Beuth Hochschule für Technik, Berlin

BEUTH HOCHSCHULE FÜR TECHNIK BERLIN
University of Applied Sciences

ulm university universität ulm

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

www.embryotox.de

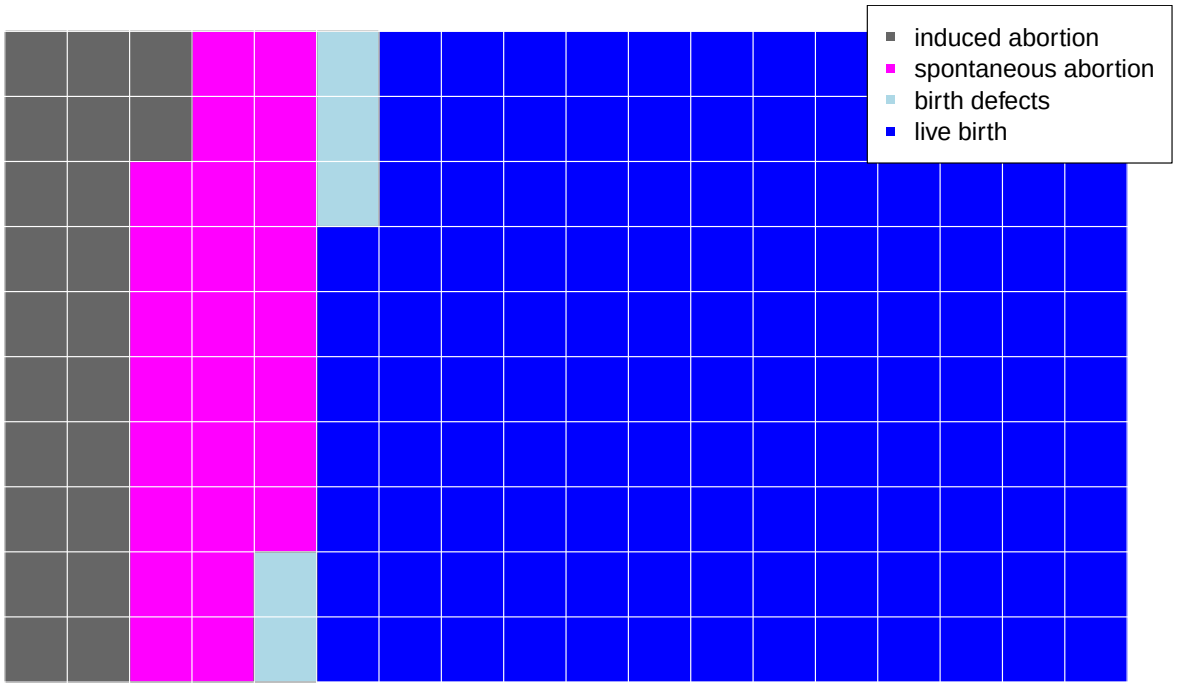
Agenda

Towards demonstration of time specific effects of discontinued exposure:

- Pregnancy outcome – basics
- The German embryotox cohort
- Analyses for permanent and for time-dependent exposure
- Modeling non-continuous exposure
- Summary

Pregnancy – not without risk

Data DESTATIS(2011)



each of the 180 squares represents 5.000 pregnancies

662.685 live births, thereof *25.000* with birth defects $\approx$ 3-5%

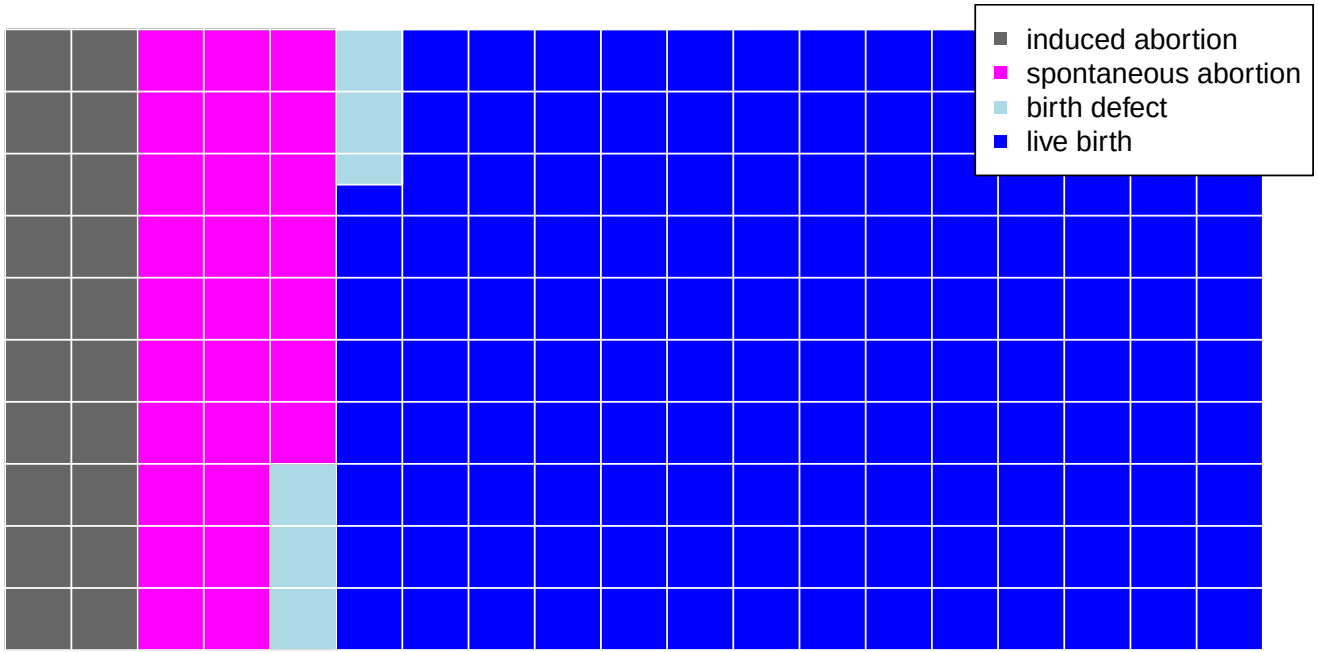
108.915 induced abortions

130.000 spontaneous abortions $\approx$ 15-16%

900.000 total

Pregnancy – not without risk

Data DESTATIS(2014)



each of the 190 squares represents 5.000 pregnancies

714.900 live births, thereof *27.500* with birth defects $\approx$ 3-5%

99.715 induced abortions

135.000 spontaneous abortions $\approx$ 15-16%

950.000 total

The German Embryotox Cohort

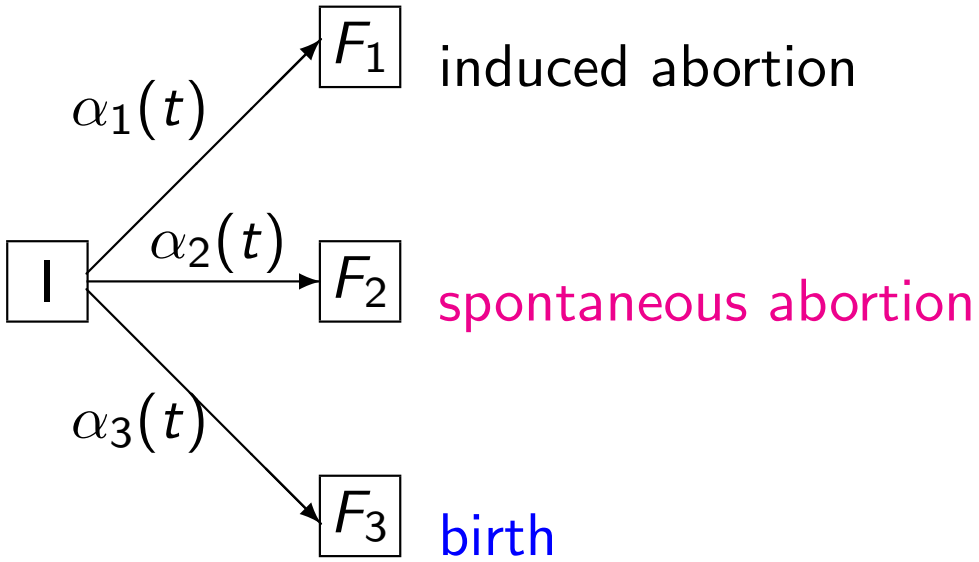
www.embryotox.de – background and facts

- The Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy works since 1988. Founding member of ENTIS.
- Provides counselling on drug risks in pregnancy and lactation by highly qualified medical/pharmaceutical academics.
- Runs a database ($>$ 40.000 completed cases) of pregnancy outcome with prospectively ascertained information on anamnestic features, exposure information etc. sampled before outcome of pregnancy is known.
- Performs studies according to good practice for clinical epidemiology.
- The internet platform is a link to statistics in practice, giving independent information on drug risks for $>$ 400 common medicinal products. (currently 6000-8000 visitors/day)

Schaefer C, Ornoy A, Clementi M, Meister R, Weber-Schoendorfer C. Using observational cohort data for studying drug effects on pregnancy outcome - Methodological considerations. Reprod Toxicol 2008; 26: 36-41.

Communicating risk – counselling and online information

Pregnancy Outcome – competing risks



States and transitions in a multistate description of pregnancy outcome.

The rates $\alpha_k(t)$ are the *driving forces*. Cumulative incidence for a certain final state may be influenced by transitions to competing states. The functions $F_k(t)$ are called cumulative incidences. In this paper we concentrate on F_2: spontaneous abortion.

Estimation and Inference – one sample case

- data
  event time T and an event type $k = 1, \ldots, K$
- cumulative incidence functions
  $F_k(t) := P(T \leq t, \text{cause} = k)$
- marginal distribution function
  $P(T \leq t) = 1 - S(t) = \sum_k F_k(t)$
- estimation based on data in the risk set ($\rightarrow$ left truncation)
  $\widehat{F_k}(t) = \sum_{i|t_i' \leq t} \widehat{\alpha}_k(t_i')\widehat{S}(t_i'-), \alpha_k(t)$ cause specific hazard
  $S(t)$ all cause survival

Computations see **R** package etm

Meister R, Schaefer C. Statistical methods for estimating the probability of spontaneous abortion in observational studies. – Analyzing pregnancies exposed to coumarin derivatives. Reprod Toxicol 2008; 26: 31-35.

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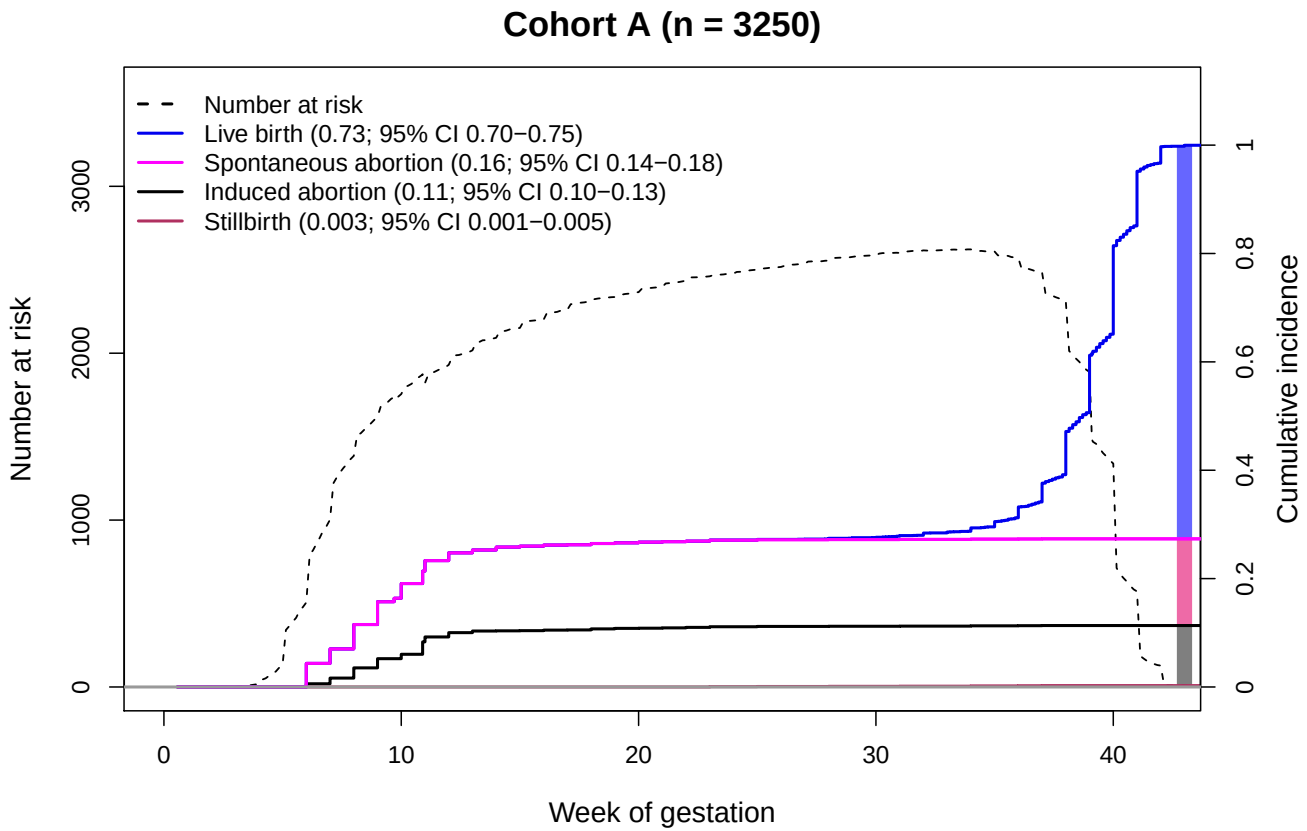
Beyersmann, J., Allignol, A., and Schumacher, M. (2012). Competing Risks and Multistate Models with R. Springer, New York.

Pregnancy Outcome – competing risks and left truncation

Avoid length bias



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Embryotoxic Effects – principles

Paracelsus (1538) Septem Defensiones

Wenn ihr jedes Gift recht auslegen wollt, was ist, das nit Gift ist? Alle Dinge sind Gift, und nichts ist ohne Gift; allein die dosis machts, daß ein Ding kein Gift sei.(Wiki)

Embryotoxicity is special!

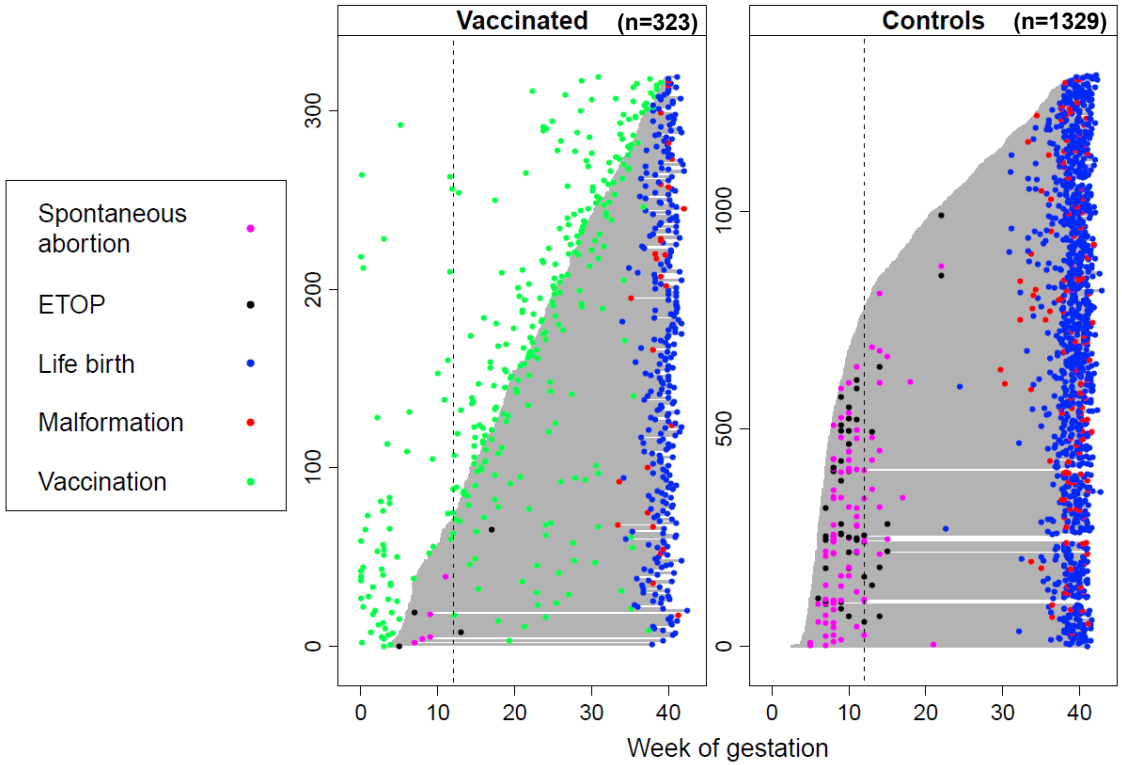
Paracelsus paradigma update – The Thalidomide tragedy

- Dose is not the sole determinant of toxicity.
- Susceptibility varies with gestational age.
- There are organ-specific critical periods for birth defects in humans Lenz (1962), Nowak (1965) ($n = 88$ cases).

In pregnancy, susceptibility for certain effects is not constant, due to embryonic development and changes in maternal conditions.

A-(H1N1)v2009 Vaccination – change of exposure

Avoid time dependent bias

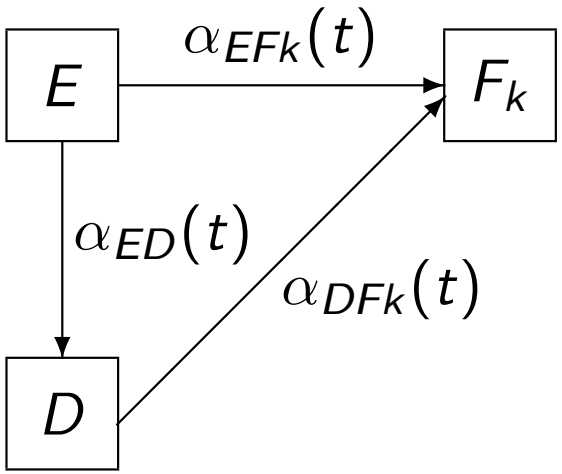


No increased risk for spontaneous abortion after vaccination observed. Analysis using a cause specific Cox-model, with vaccination as time-dependent covariate.

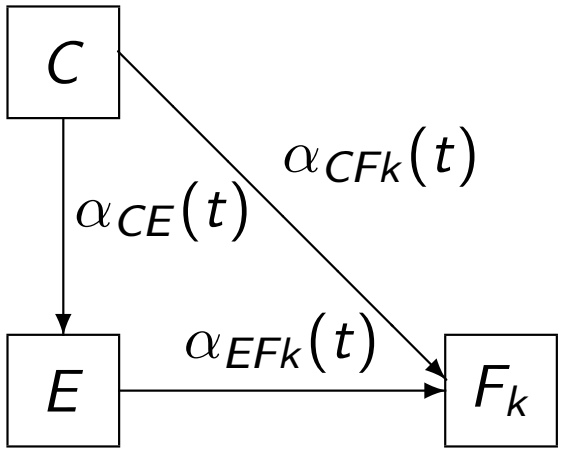
Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, Schaefer C. A-(H1N1)v 2009: A controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine 2012; 30: 4445-52.

Non Continuous Exposure – a multistate approach

Multiple final states (competing risks)
transient exposure states



continuous exposure

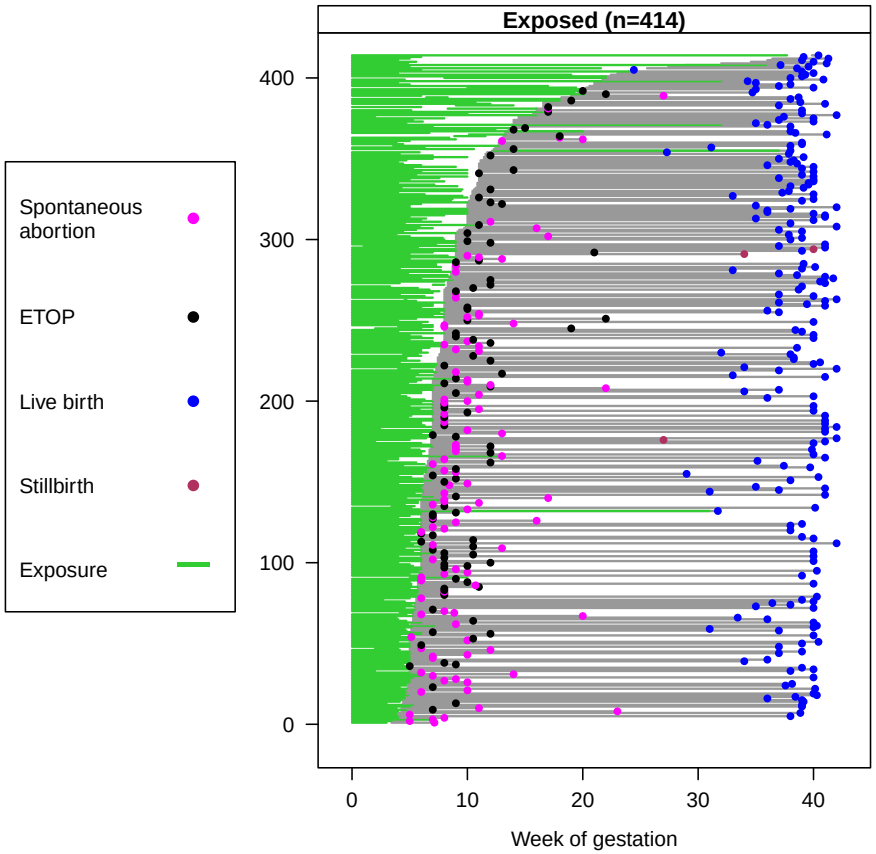


single application

C: no exposure, control E: exposed D: exposure discontinued

F_k: final state $k =$ induced abortion, spontaneous abortion, birth

Discontinued Exposure – new data on anti-coagulants



Cause specific Cox model
time dependent discontinuation $d(t)$

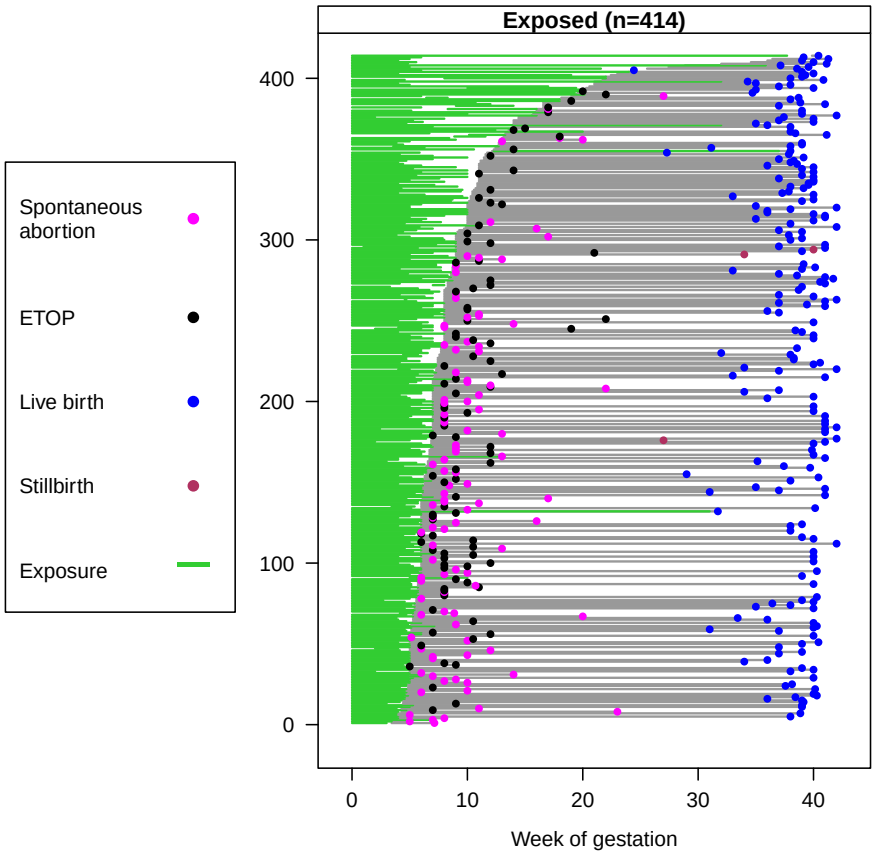
start	stop	state	d(t)
t_{entry}	t_d	cens	0
t_d	t_{exit}	$O(t_{exit})$	1

Counting process notation of time dependent covariates n=414.

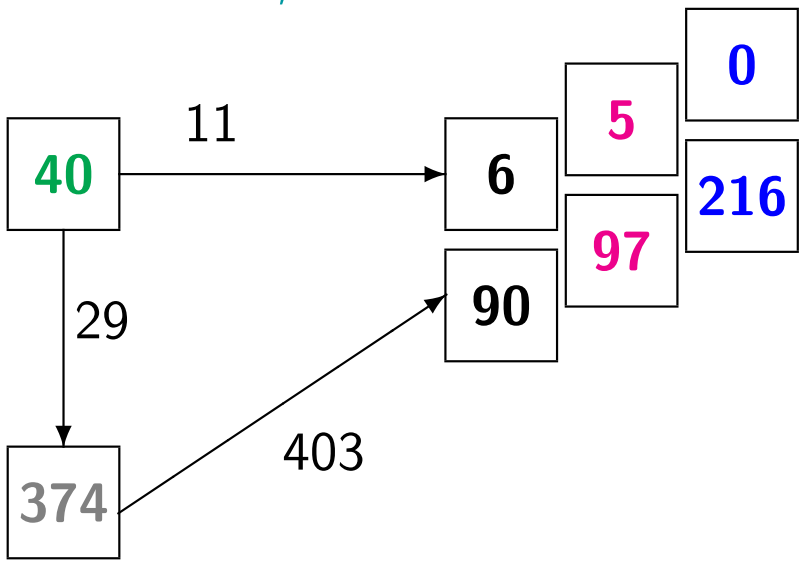
HR* (95% CI): 1.62(0.65, 4.05)
*: reciprocal

```
fit.d <-coxph(Surv(start,stop,state==2)~ d,data=counting)
```

Discontinued Exposure – exposure and transitions



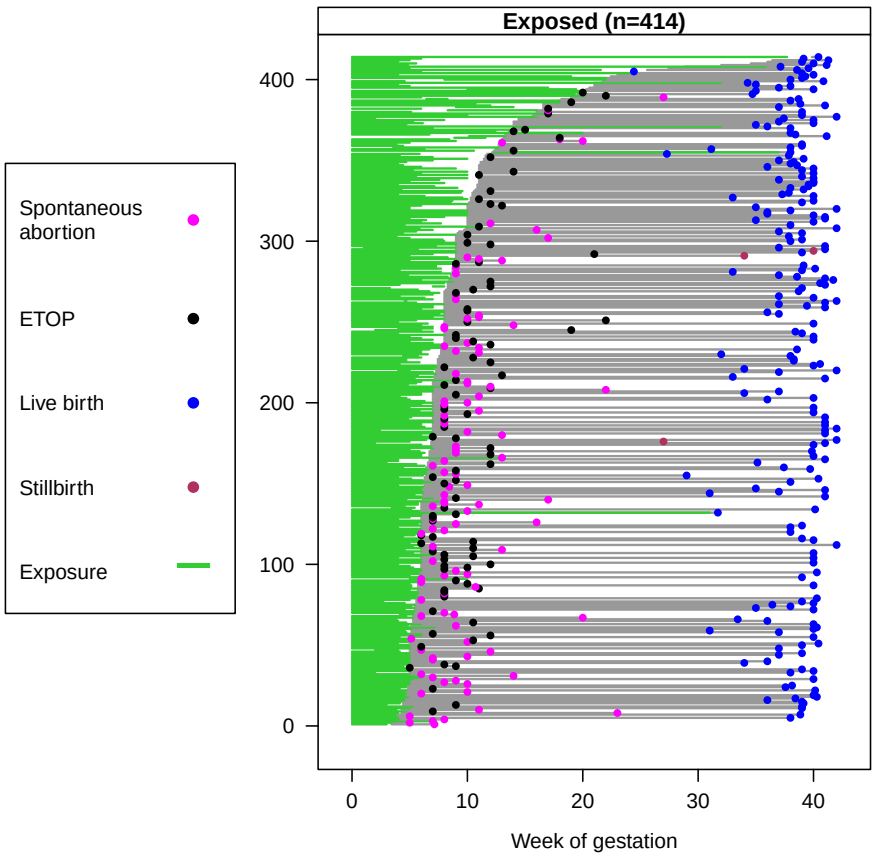
Marginal frequencies in exposure, transitions, and final states.



– majority of pregnant women enter the study after discontinuation
– joint Cox model with discontinuation time not feasible

(no conditioning on the future)

Discontinued Exposure – discontinuation time



Cause specific Cox model using discontinuation time $t(d)$

start	stop	state	t(d)	d(t)
t_{entry}	t_{exit}	$O(t_{exit})$	t_d	1

Only observations with discontinued exposure used n=403

HR (95% CI): 1.14(1.02, 1.27)

```
fit.td <-coxph(Surv(start,stop,state==2)~ t.d,
               data=subset(counting,d==1))
```

Time Dependent vs Time Specific – first experiences

Anticoagulants (n=414) and low dose MTX (n=197)

	time-dependent			time-specific		
	HR	95% CI		HR	95% CI	
Coumarin	1.62	0.65	4.05	1.14	1.02	1.27
Methotrexate	3.86	1.52	9.83	0.99	0.81	1.21

Spontaneous Abortion: results varying between substances

	time-dependent			time-specific		
	HR	95% CI		HR	95% CI	
Coumarin	2.62	1.12	6.01	1.39	1.25	1.54
Methotrexate	0.64	0.08	4.91	1.33	1.20	1.46

Elective Termination: interpretation to be done

Weber-Schoendorfer et al. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheumatol. (2014)

Results and points to consider

- Event-history methods allow bias-reduced estimation of spontaneous abortion rates when accounting for left-truncation and competing risks.
- Lenght bias and time-dependent bias can be reduced (removed?).
- Estimation of time-specific effects of exposure state is feasible within the proportional hazard framework.
- Communication of results and problems has to be addressed.
- Caveat! Tacitely non-informative left-truncation is assumed.
- Caveat! Informative left-truncation – can adjustment reduce effects?
- Caveat! What is the rôle of competing outcomes?
- Alternatives to Cox regression – regression of pseudo residuals?

Acknowlegdement

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Maria Hoeltzenbein, Stefanie Padberg, Evelin Wacker (all Charité Berlin), and Martin Schumacher (Univ. Freiburg) for hints on time-specificity, their encouragement and very helpful discussion of our approach.

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