Risk Communication on drugs in pregnancy – an evolving landscape

Prof. Alice Panchaud

01.09.2023 – ENTIS meeting 2023

Conflicts of interest – Ongoing Grants

Grant Swiss National Commission for Quality (327'936 CHF) 2023-26 – "Digital platform for HYpertensive Patient Reported OutcoMes – HYPROM". PI A. Panchaud

Grant Fonds paritaire RBP IV & pharmaSuisse (223'000 CHF) 2023-24 – "MyCareStart pilot study in a cohort of primary care pharmacists in Switzerland considered early adopters". PI A. Panchaud and M. Voirol.

European Medecine Agency EMA/2017/09/PE (Lot 3) (121'000.- Euro) 2021-24 – "Safety monitoring of COVID-19 vaccines in the EU". PI Prof. Miriam Sturkenboom, University Medical Center Utrecht.

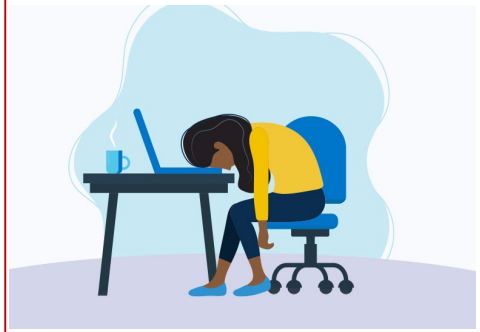
Federal Office of Public Health (207'000 CHF) 2021-23 – "The COVI-Preg registry". PI A. Panchaud & D. Baud

EMA/2017/09/PE/11, Lot 4 (115'000.- Euro) 2020-23 - "Study on impact of COVID-19 infection and medicines in pregnancy". PI Prof. Miriam Sturkenboom, University Medical Center Utrecht.

H2020-Grant (487'206.- CHF) – 2019-24. ConcePTION "Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimized evidence generation". PI Prof. Miriam Sturkenboom, University Medical Center Utrecht.

Conflicts of interest – mindset and education

- Loving negative results when reading or publishing safety studies on medication in pregnancy and breastfeeding !



Standard researchers

Me

- Practicing risk communication daily but not trained intensively for it.

Risk

What is risk?

What is a risk?

Attempt to define risk

- Possible danger, more or less foreseeable, inherent to a situation or activity
- Uncertain eventuality because it is not systematic
- Harmful event
- Absent if the behavior or situation that generates it is avoided (well, … not increased if… with Birth defects)
- …

What is a risk?

Risk level

- Based on the impact of the risk
- Based on probability of risk occurrence
- Based on available prevention or treatment measures when it occurs
- …

What is unsafe?

A moving target

- Clinical context and relationship with a given risk on the part of patients
- Relationship with a given risk on the part of healthcare providers
- Risk perception by all involved stakeholders but proper risk communication should mitigate this variable
- Available scientific evidence on a risk
- …

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Big Data

What is evolving in risk communication?

Evolution of safety data sources

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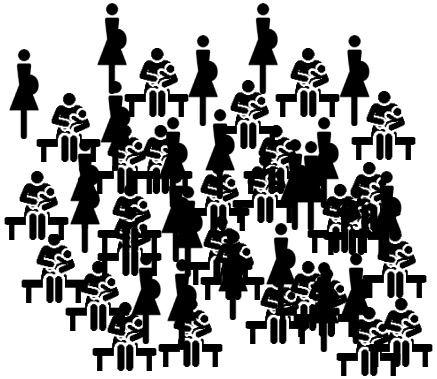
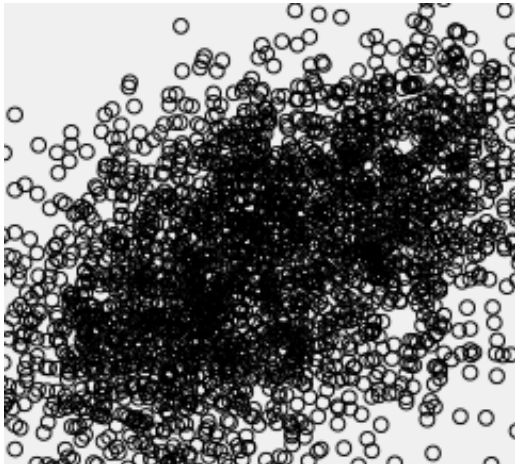




No data

Case report, case series

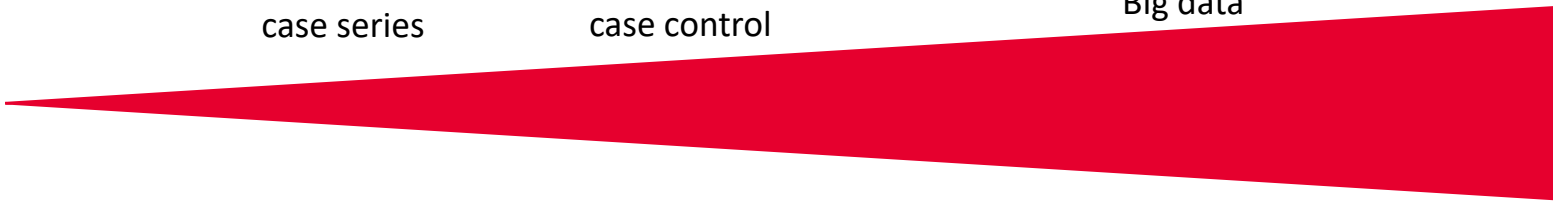
Traditional cohorts, case control

Big data

Increasing sample sizes, IT needs and statistical complexity

Evolution of risk communication

No data	Case report, case series	Traditional cohorts, case control	Big data
….Risk assessment is not possible with the available data. Baseline risk of major birth defects is 2-3% depending on the population studied. Evidence is reassuring for most of the assessed medication….	…Risk estimates allow to exclude a twofold or … of the baseline risk Risk estimates provide a risk of 4% compared to the 2-3% baseline risk. After exposure, 96 healthy infants out of 100 compared to 97-98…	?	



Increasing sample sizes, IT needs and statistical complexity

Evolution of risk communication

Big Data

What is Big Data?

Big Data – the new actor in the game

Big data - Pros

- What is big data?

A basic definition of big data includes "**the 3 Vs**":

- **variety** with the linkage of many data sets from heterogeneous independent sources in a single data set
- **volume** with the large number of observations and variables per observation from different sources
- **velocity** with real-time or frequent data updates, often fully or partially automated.

Clin Epidemiol. 2017; 9: 245–250.
Journal of Data Analytics, Vol 1, No 1, (2022), 1-7

Big Data – the new actor in the game

Big data - Pros

- We can no longer do without it.

  It offers an effective solution with respect to cost, number of pregnancies included, some validity issues (e.g., no recall bias), and generalizability (i.e., population-based).

  It has firmly established itself in the health research,[1,2] illustrated by publications in high-ranking general-interest biomedical journals, such as The New England Journal of Medicine, JAMA, Journal of Internal Medicine, Science, and Nature.

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Big Data

What are the problems with Big Data?

Evolution of safety data sources

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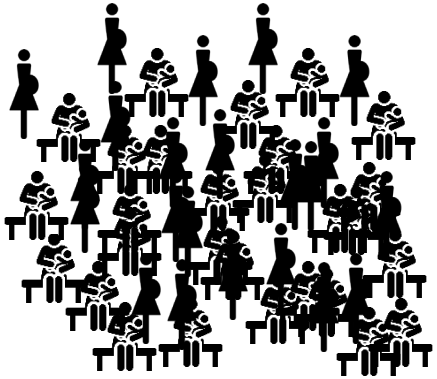

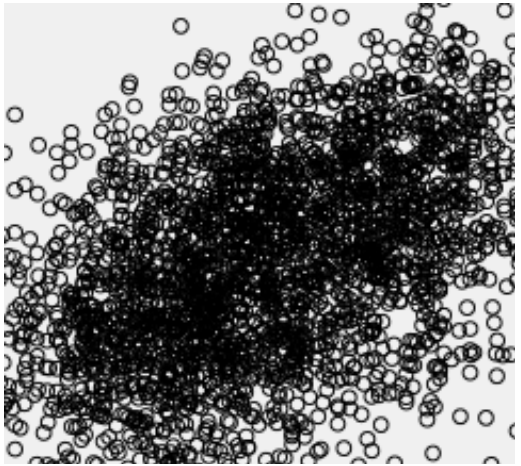

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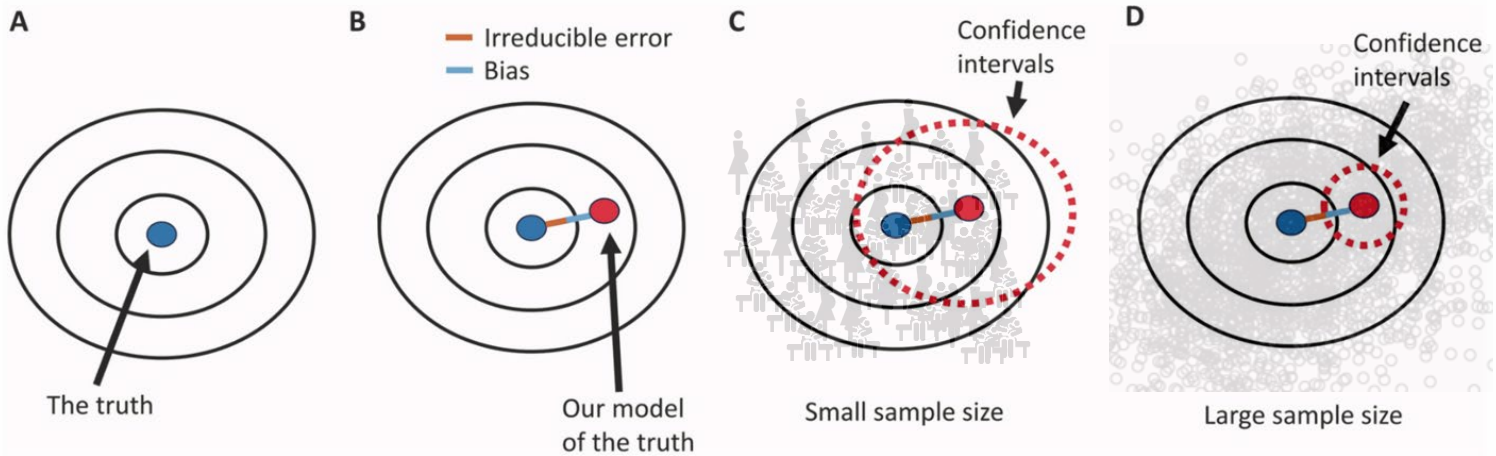
Increasing sample sizes, IT needs and statistical complexity

1. Big Data paradox



Traditional cohorts, case control

Big data

Cancer investigation 2022, vol. 40, no. 7, 567–576

1. Big Data paradox

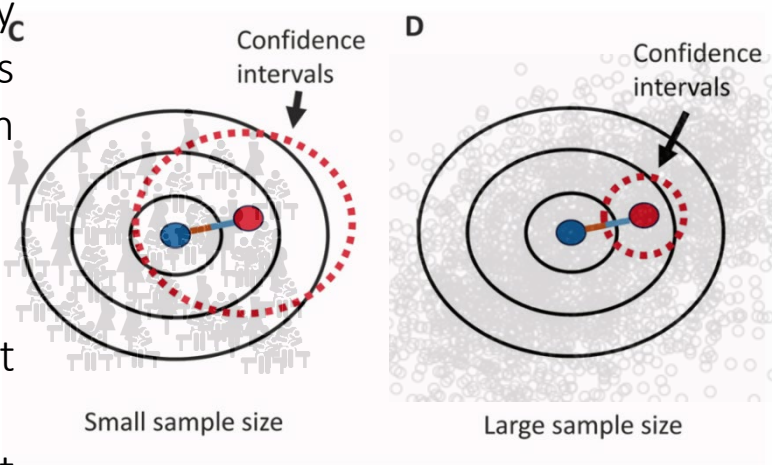
Counterintuitively, as the size of a study increases, the probability that its confidence intervals will include the truth decreases.

Three potential strategies to mitigate it:

(1) improving data quality;

(2) anticipating and modeling patient heterogeneity;

(3) including the systematic error, not just the variance, in the estimation of error intervals.



Traditional cohorts, case control

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Cancer investigation 2022, vol. 40, no. 7, 567–576

1. Big Data – distortion of risk estimates

Big data - Cons

Big data comes with **limitations** that can **threaten their validity and provide distorted risk estimates**, misleading the benefit-risk assessment of a drug in pregnancy.

- **Exposure and outcome misclassifications** are one of the important limitations as information on "if "and "when" a drug has been taken is almost never available (e.g., unused dispensing, use of old prescription, drug sharing, use after the relevant etiological period), as using billing or diagnostic codes to define outcomes in claims is not straightforward.
- **Lack of control for unmeasured confounders.** Confounding by indication and other risk factors are other important limitations as these databases usually lack information on behavioral and lifestyle habits (e.g., smoking, alcohol use, physical exercise) and outpatient health service utilization (e.g., over the counter drugs).

1. Big Data – distortion of risk estimates

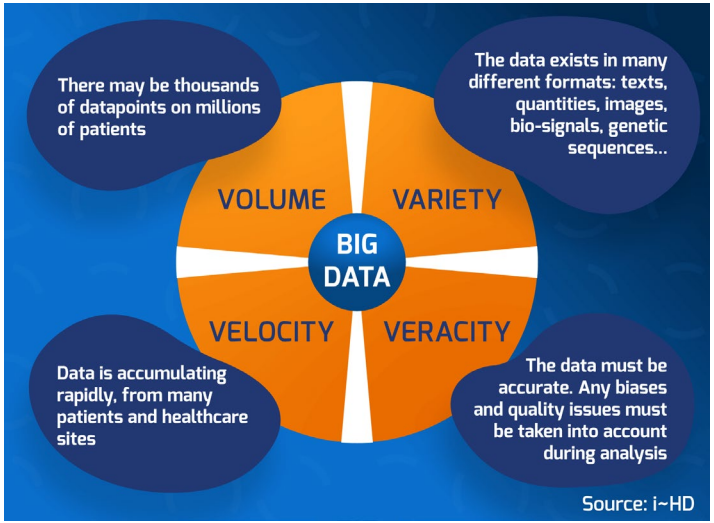
Big data - Cons

"volume" V linked to precision but not necessarily to validity (the "veracity" V in the big-data vocabulary).

Plausible hypotheses, expert knowledge, and accurate measurement tools must be available to ensure validity of research findings,

↓

a highly precise biased result, especially perceived as credible based on precision alone, is more dangerous translated into clinical practice than an imprecise biased result.



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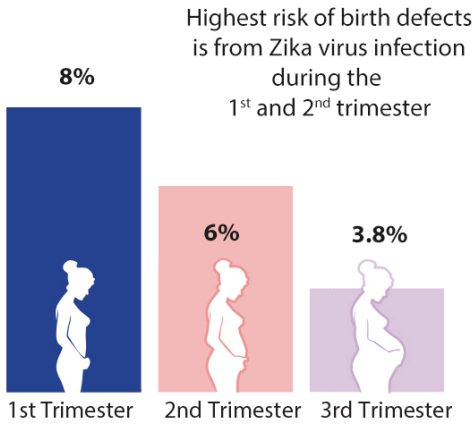
2. Big Data – effect size

Difference between two means	Original units	The average patient satisfaction increased last year by 0.5, from 3.1 to 3.6 in a 1 to 5 scale.
Risk	Units-free	The risk that a child has a major birth defect at birth is 1/45 or 2.2%.
Relative risk	Units-free	A newborn exposed to carbamazepine in utero is 1.25 times as likely as a unexposed newborn to have a major birth defects (mainly spina bifida) at birth.



Effect is the quantity of interest i.e., the difference in group means or the correlation, or whatever measure that conveys the magnitude of the phenomenon of interest.
An *effect size* is simply the amount of that quantity—or the magnitude of the effect.

https://www.cdc.gov/pregnancy/zika/data/index.html

Effect size – Quiz

Imagine two randomized clinical trials comparing new treatments for pneumonia.
Both trials produce statistically significant results at exactly $p = 0.05$.

Which treatment should be preferred, A or B?

RCT trials compared **new treatment A** for pneumonia to standard care.
Sample size: **150 patients** randomized in one of the two groups
Results: produce statistically significant results at exactly $p = 0.05$

RCT trials compared **new treatment B** for pneumonia to standard of care.
Sample Size: **15'000 patients** randomized in one of the two groups
Results: produce statistically significant results at exactly $p = 0.05$

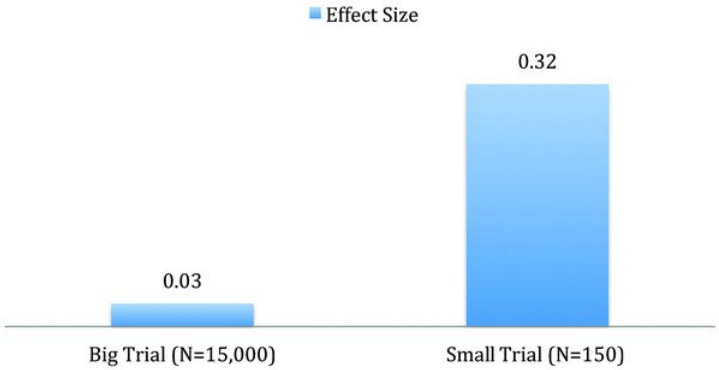
2. Big Data - effect size

Many people would prefer the treatment based on the larger trial.

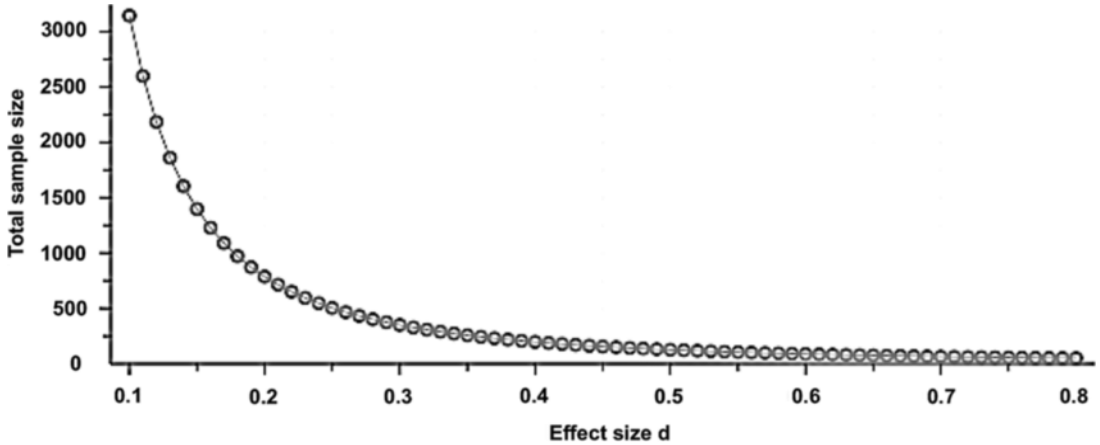
However, the effect size for the smaller trial would need to be significantly larger in order to achieve the same $p = 0.05$ significance level.

At a constant p level, effect size declines as a function of sample size.

In other words, the number needed to treat would be considerably smaller for the treatment evaluated in the small trial.



2. Big Data - effect size



Sample size calculation: Significance level alpha is set at 0.05. Power is set at 0.8. The effect size (calculated from expected difference between groups and standard deviation) is given on the x-axis, and the calculated sample size is given on the y-axis. **Decreasing the effect size drastically increases the sample size needed for the experiment.**

Langenbeck's Archives of Surgery (2022) 407:529–540

Nurs Res. 2021 May-Jun; 70(3): 222–230.

2. Big Data – clinical relevance

An important issue to consider is what magnitude of observed effect would be deemed “clinically relevant.” This interpretation is of course dependant on the outcome of interest.

(a) research findings are significant, but not clinically relevant (risk or no risk?);

(b) research findings are both clinically relevant (observed risk) and significant;

(c) research findings are clinically relevant (potential risk), but not significant;

(d) research findings are neither clinically (no risk) relevant nor significant.

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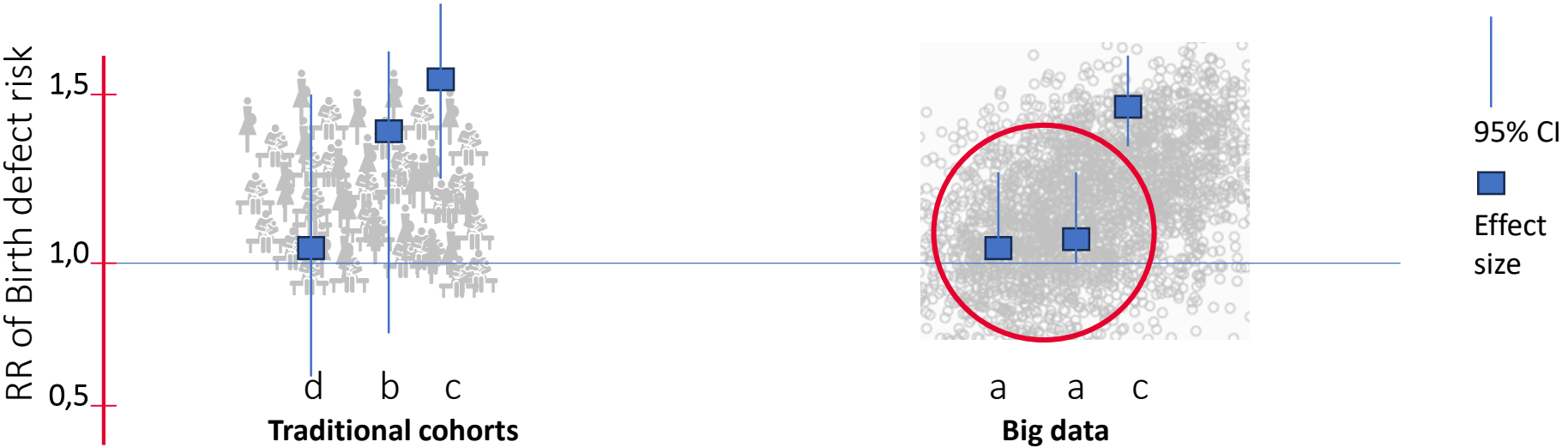
2. Big Data – clinical relevance



(a) research findings are significant, but not clinically relevant;

(b) research findings are clinically relevant, but not significant;

(c) research findings are both clinically relevant and significant;

(d) research findings are neither clinically relevant nor significant.

2. Big Data – clinical relevance

An important issue to consider is what magnitude of observed effect would be deemed “clinically relevant.”

(a) research findings are significant, but not clinically relevant;

? challenging risk communication

(b) research findings are both clinically relevant (observed risk) and significant;

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Big Data

How am I doing risk communication with small effect size and/or high risk of residual confounding?

Evolution of risk communication

1. Communicating upfront small effect size and/or high risk of residual confounding for a treatment with a benefit for her health

-> I often choose not to mention it to simplify the message, especially when there is already a lot of evidence to discuss.

Big data

Increasing sample sizes, IT needs and statistical complexity

Evolution of risk communication

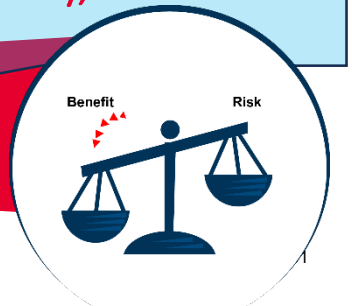
2. Patient asking about a study with small effect size and/or high risk of residual confounding for a treatment with a benefit for her health

Residual confounding: the amount of the data doesn't allow us to be as accurate as we would like to be (data not completely "cleaned"). Small effects (i.e. RR of 1,01-1,1) likely due to other things then the exposure to the medication itself.

Clinically irrelevant effect size: Big data studies are like looking with a microscope, they can see bumps in the road that you would not feel in your car. These effects are most probably irrelevant for your and your babies 'health.

✓ Mention other studies with different results if available. Most importantly, discuss the effect of a suboptimal management of the disease.

Big data



Increasing sample sizes, IT needs and statistical complexity

Evolution of risk communication

Patient asking about a study with small effect size and/or high risk of residual confounding for a treatment with very little or no benefit for her health

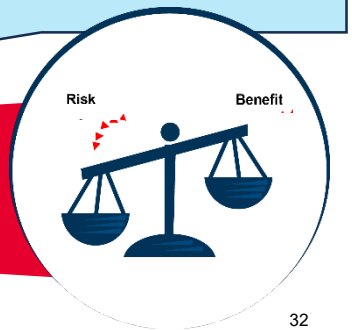
No other studies with different results.

-> We cannot conclude that this medication is at risk for your pregnancy. However, the expected effect for your health is not sufficient to take any risk.

Other studies with different results.

-> The expected effect of this treatment for your health is not sufficient to take any risk.

Big data



Increasing sample sizes, IT needs and statistical complexity

Evolution of risk communication

Remember the basics

You are a translator of the available evidence.

The patient is the one who makes the final choice.

No data

Case report, case series

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In a nutshell

- In the era of big data, safety assessment of medications in pregnancy is facing completely new challenges.
- These big data studies provide some of the needed evidence base to treat pregnant women with confidence, but they are also systematically associated with methodological issues due to their observational nature and the underlying data structure.
- Weak risk associations for specific or pooled malformations, typically minor effect sizes but with confidence intervals excluding the null, are now commonly reported for many intensively studied drugs (e.g., SSRIs, paracetamol).
- With these limitations, it seems obvious that slight increases in risk (i.e., relative risk/odds ratio between 1.01 and 1.2) observed in studies using, e.g. healthcare utilization databases, should be interpreted with great caution.
- Balancing with the benefits of the treatment for your patient and the benefit/risk of alternatives often helps navigate through this new landscape,… like in the old days.

Thank you for your attention