Supporting Safe and Effective Medicines Use in Pregnancy and Breastfeeding

Balancing Benefit and Risk

20th May 2026

Brian Cleary & Nicola Maher

THE ROTUNDA HOSPITAL DUBLIN

IMPS Irish Medicines in Pregnancy Service

Medication use in pregnancy and breastfeeding – A challenging area

- Medication use is common among pregnant and breastfeeding women
- Medication use is complex – Considerations for mother and infant
- Potentially serious implications for mother and baby
  - Maternal morbidity and mortality
  - Adverse pregnancy outcomes
- Lack of information about medication safety in pregnancy and breastfeeding
- Medication management issues may contribute to maternal deaths

Key Challenge: Balancing maternal benefit and fetal/neonatal risk

Cardiac arrest

Autoimmune conditions

Endocrine

Cancer

Renal failure

Sepsis/Infection

VTE

Pregnant women get sick and sick women get pregnant

Seizures

CVA

Psychosis

Hypertension

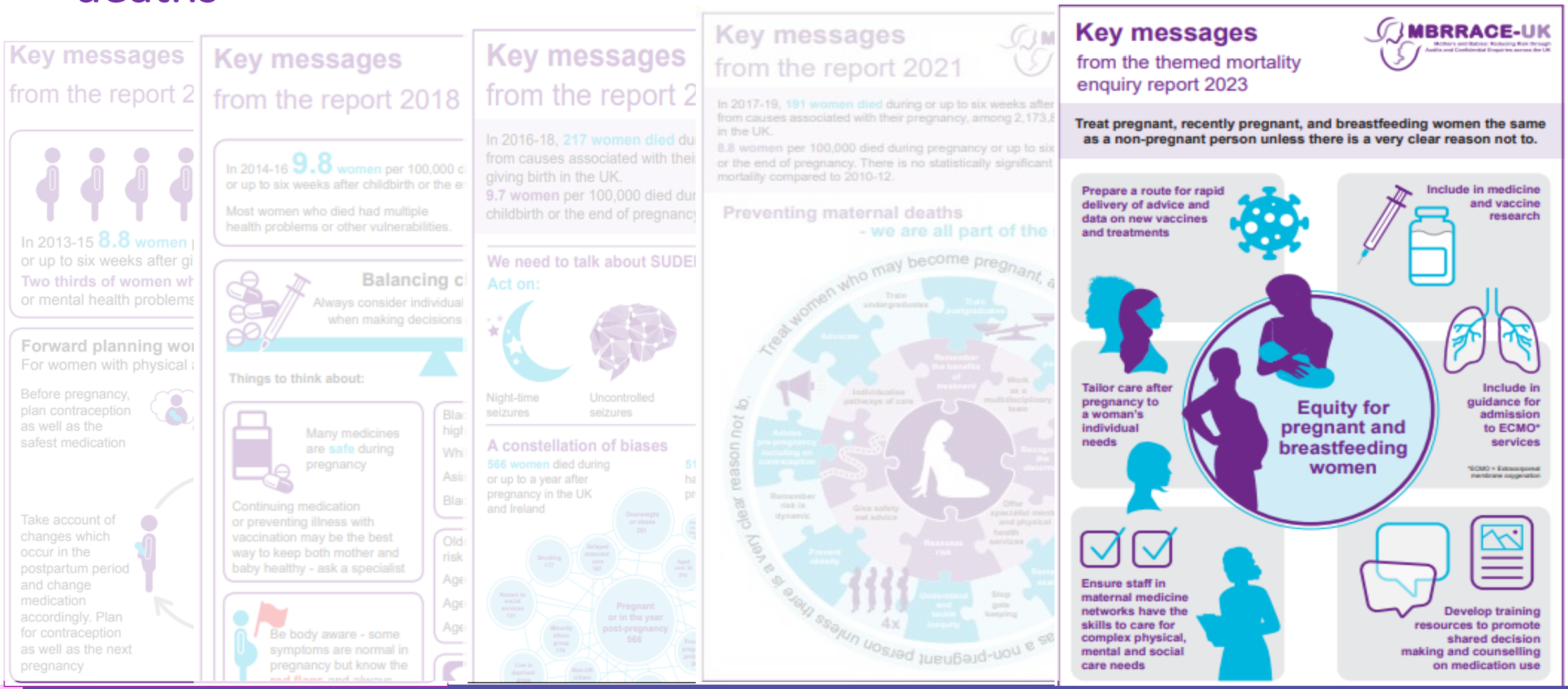
Heart failure

Caesarean section

Trauma/accidents

Mental health crisis

Medication management issues may contribute to maternal deaths



Taken from: Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidityhttps://www.npeu.ox.ac.uk/mbrrace-uk/reports/maternal-reports

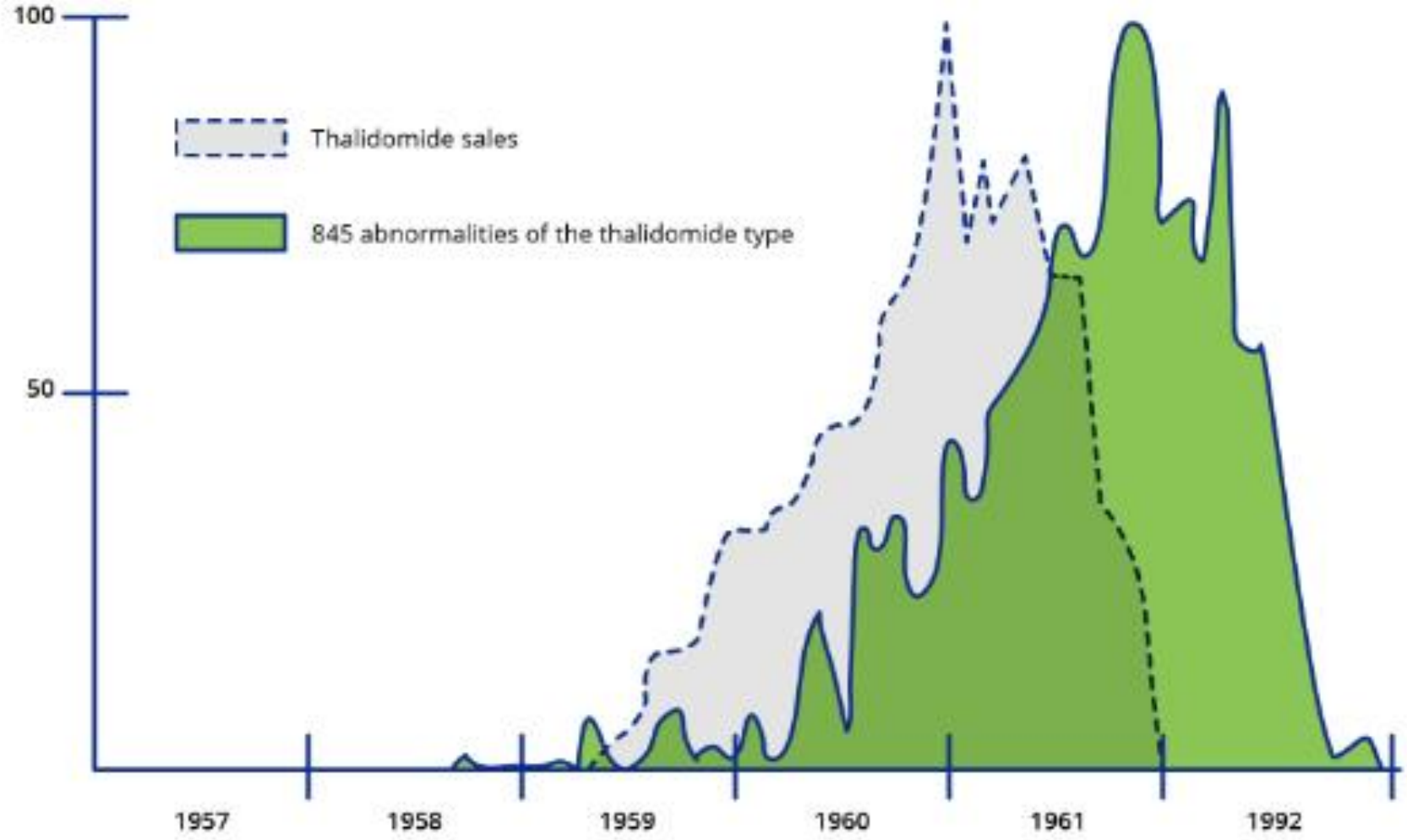
Historical context

We don't know where we are going if we don't know where we have been…

Thalidomide

- Synthesised by Grunenthal in 1954 while searching for new antimicrobial agents → Noted used to aid restful sleep.
- Licensed and marketed in up to 50 countries - Widely used in the late 1950's and early 1960's for the treatment of nausea in pregnant women.
- Initial suspicion that thalidomide may be associated with birth defects
- In early 1960's an association between thalidomide exposure in early pregnancy and a range of congenital anomalies was noted
- Thalidomide was ultimately removed form markets worldwide (some countries took longer than others).
- Estimated 10,000 babies were born effected by thalidmoide embryopathy – 40 – 50% died before their first birthday.

Thalidomide



A Modern Example – Sodium Valproate

- Antiseizure medicine initially marketed in France in the late 1960s.
- Early 1970s animal studies and initial studies suggest possibility of CM
- During 1990s evidence building about risks of CM in pregnancy
- 2000s possibility of impaired cognitive development reported
- 2010s regulatory restrictions and pregnancy prevention programme

- Strong cumulative evidence of increased risk of dose dependent major congenital malformations
  - 11% Vs. 2-3% in general population
  - Fetal valproate spectrum disorder – Pattern of major and minor malformations
- Prenatal exposure adversely affects fetal brain development.
  - Cognitive impairment and memory
  - Delays in early development (e.g. talking, walking) → 30-40%
  - Lower IQ - independent from maternal IQ
  - Increased risk of ASD (3-fold), autism (5-fold), ADHD (1.5 fold)

Valproate Exposure & Congenital Anomalies

EUROPEAN MEDICINES AGENCY
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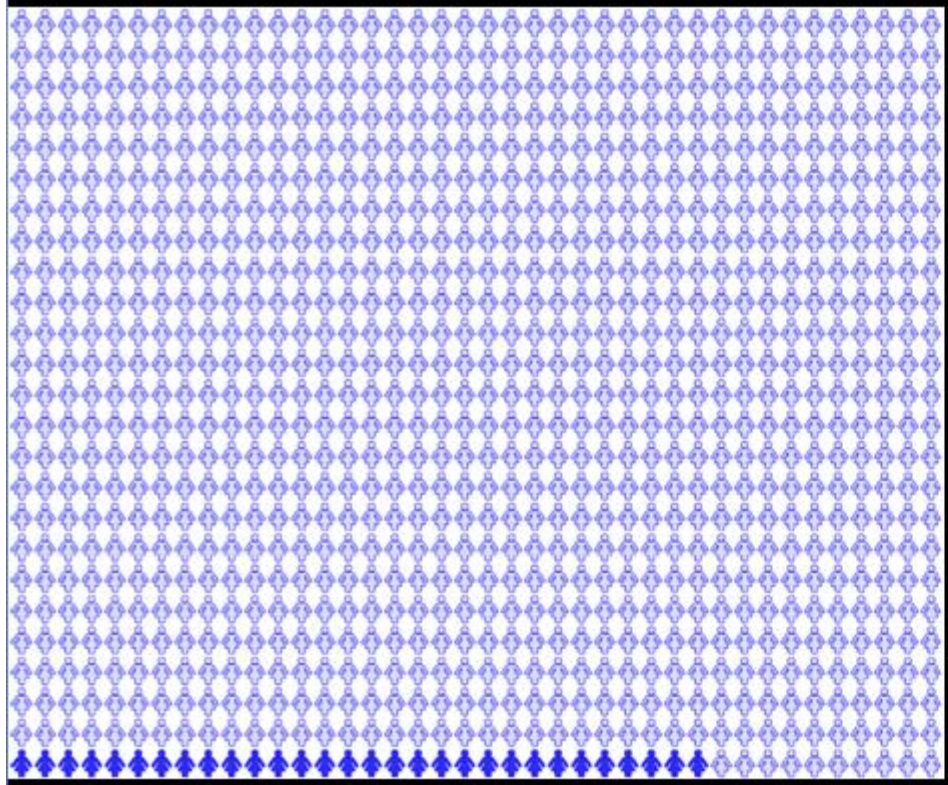
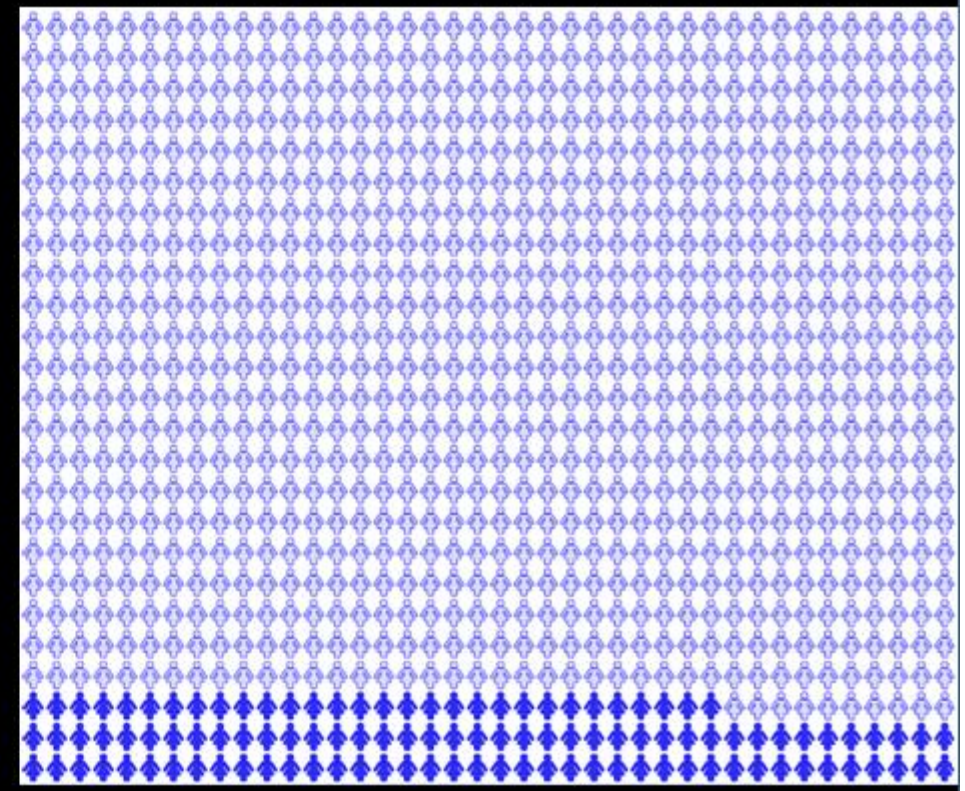
Unexposed



3%

Exposed



11%

Valproate Exposure & Autistic Spectrum Disorder

EUROPEAN MEDICINES AGENCY
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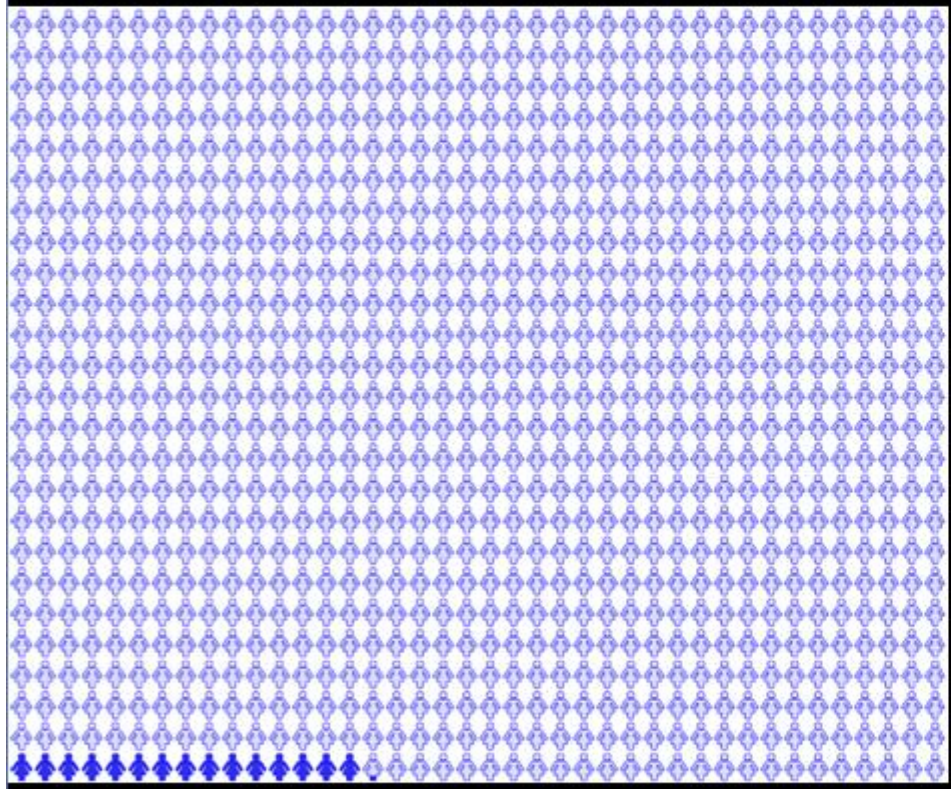
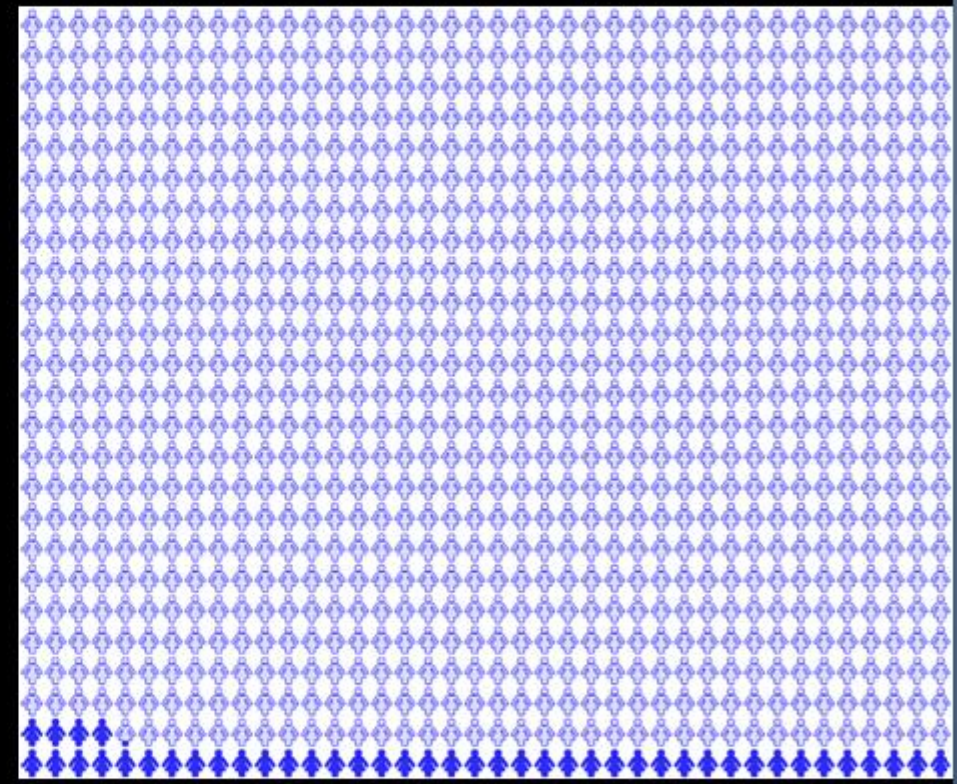


1.52%

Exposed



4.42%

Valproate Dose and Child IQ at Age 6

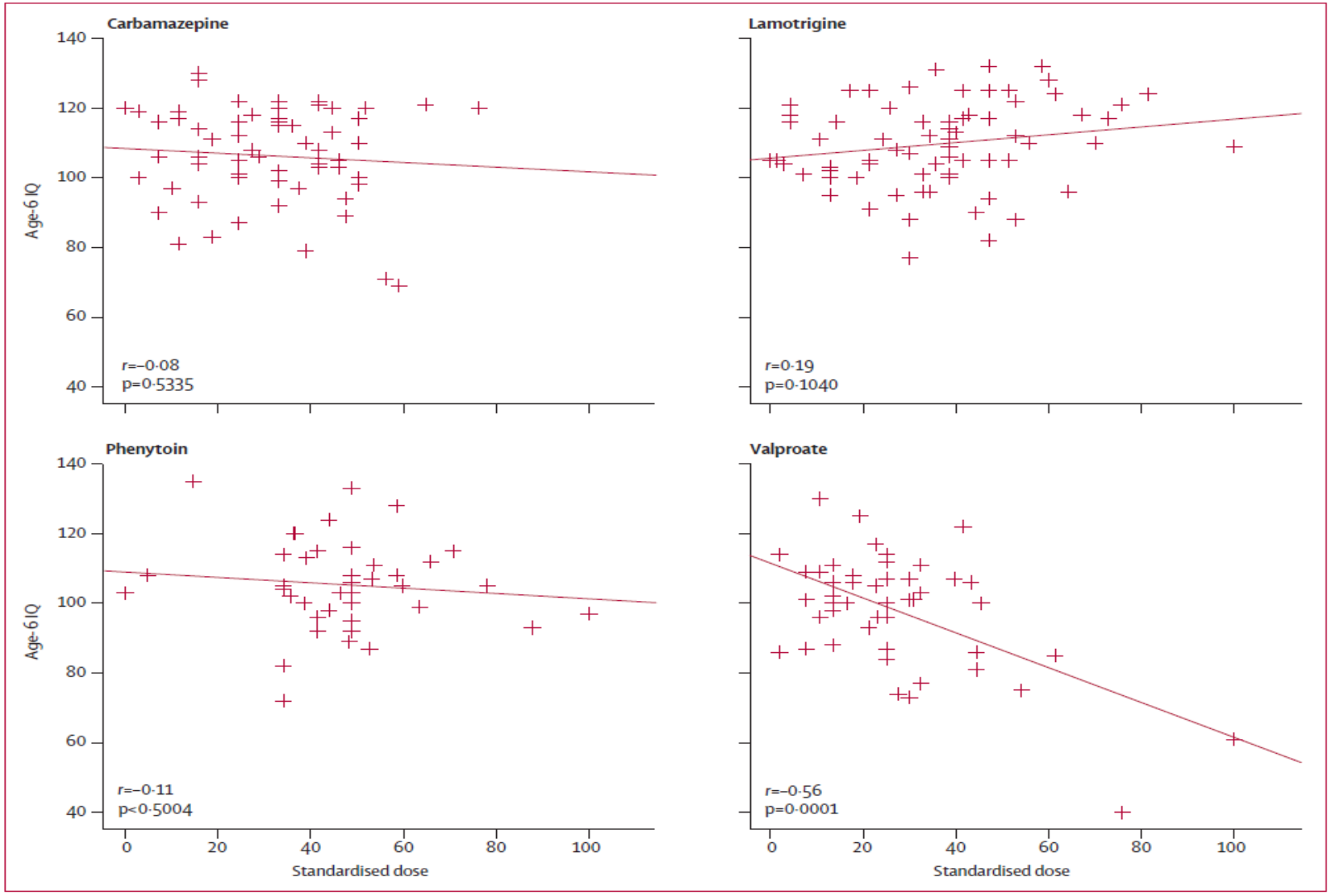


Figure 1: Relation between age-6 IQ and standardised dose of every antiepileptic drug during pregnancy

Meador et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. The Lancet Neurology 2013;**12**(3):244-52.

Relationship Between Maternal IQ and Child IQ at Age 6

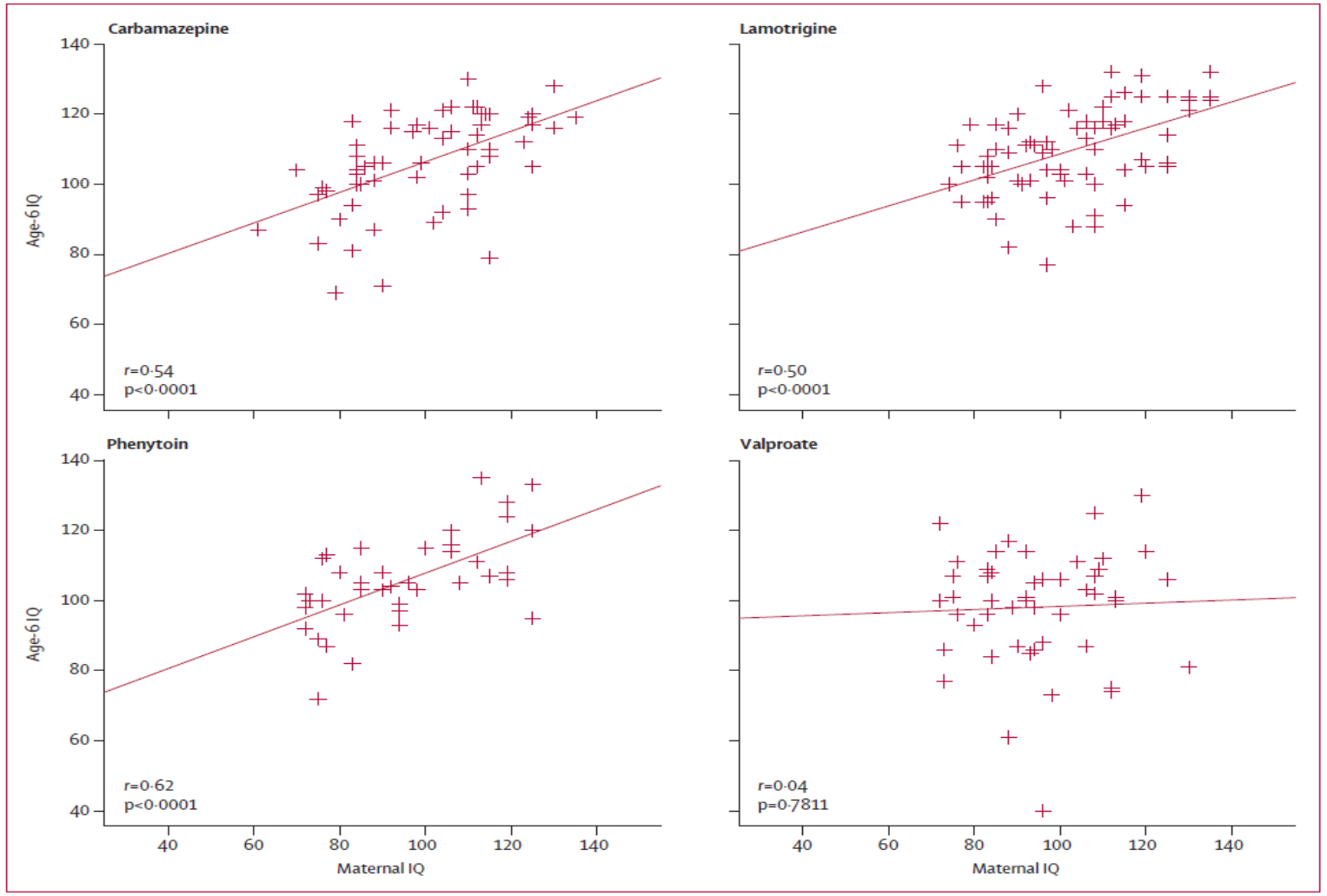


Figure 2: Relation between age-6 IQ and maternal IQ for every antiepileptic drug during pregnancy

Meador et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. The Lancet Neurology 2013;**12**(3):244-52.

Includes information on use of valproate in girls and women of childbearing potential in accordance with the pregnancy prevention program.

Also includes information on precautionary measures in **male** patients.

YOU MUST READ THIS GUIDE CAREFULLY BEFORE ANY PRESCRIPTION OF VALPROATE TO GIRLS, WOMEN OF CHILDBEARING POTENTIAL AND MALE PATIENTS

Electronic copies of this Guide and other materials related to the valproate pregnancy prevention programme can also be found online at www.hpra.ie.
Enter «Epilim» or «valproate» in the search box and then click on «EdM» next to any of the medicines that appear.

https://www.hpra.ie/homepage/medicines/special-topics/valproate-(epilim)/valproate-(epilim)---use-in-women-of-childbearing-potential-and-during-pregnancy

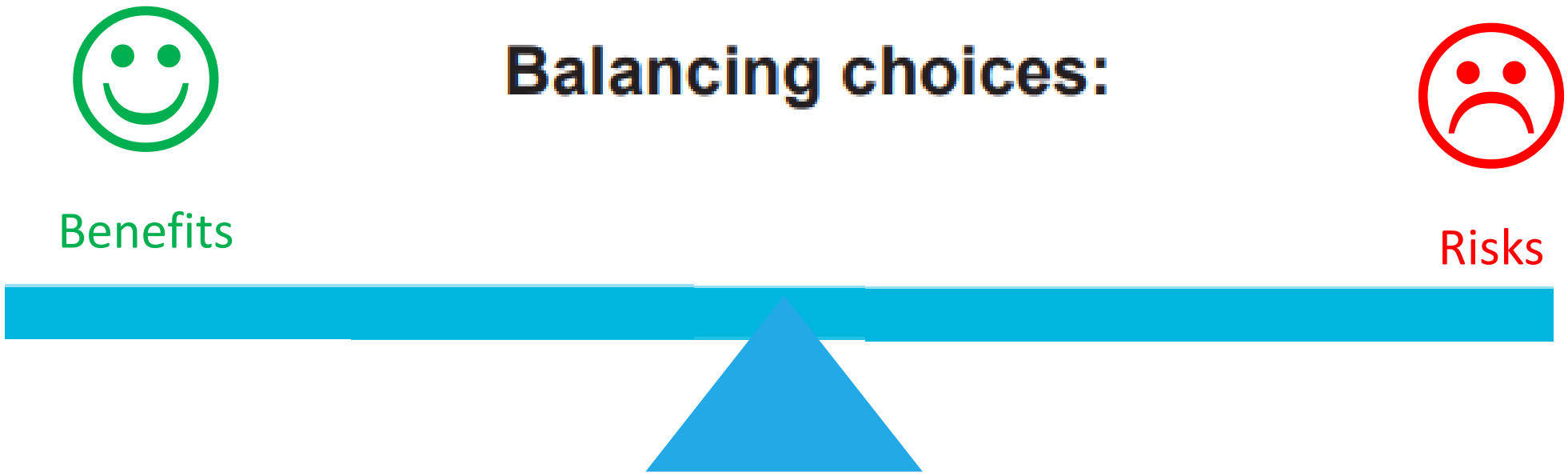
Risk – Benefit Decision Making

Risk – Benefit decision making

Balancing choices:

Always consider individual **benefits** and **risks**
when making decisions about pregnancy

Risk – Benefit decision making



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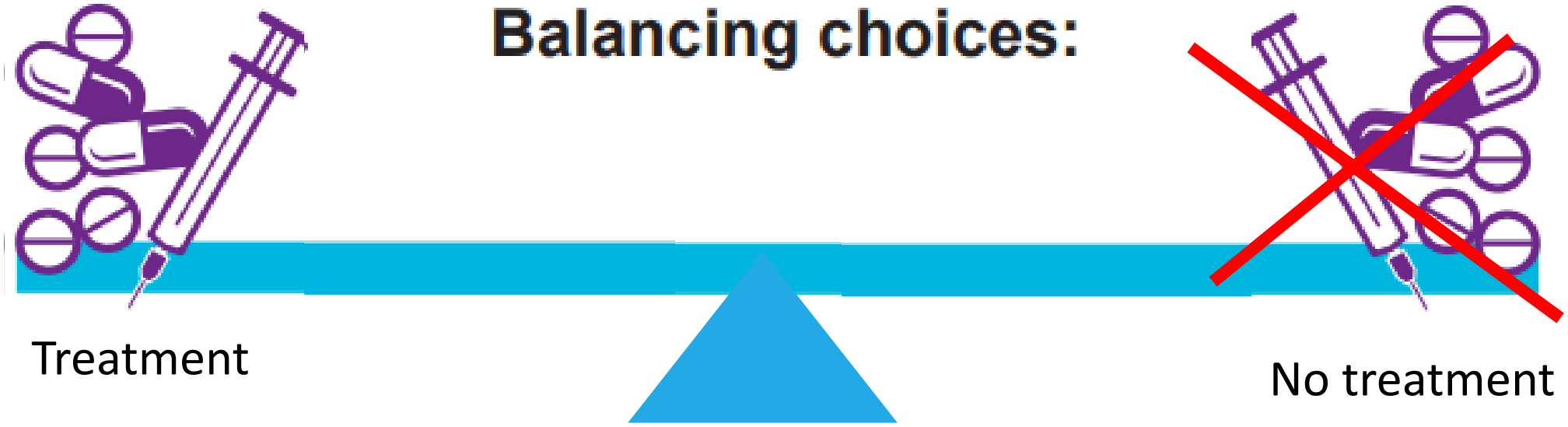

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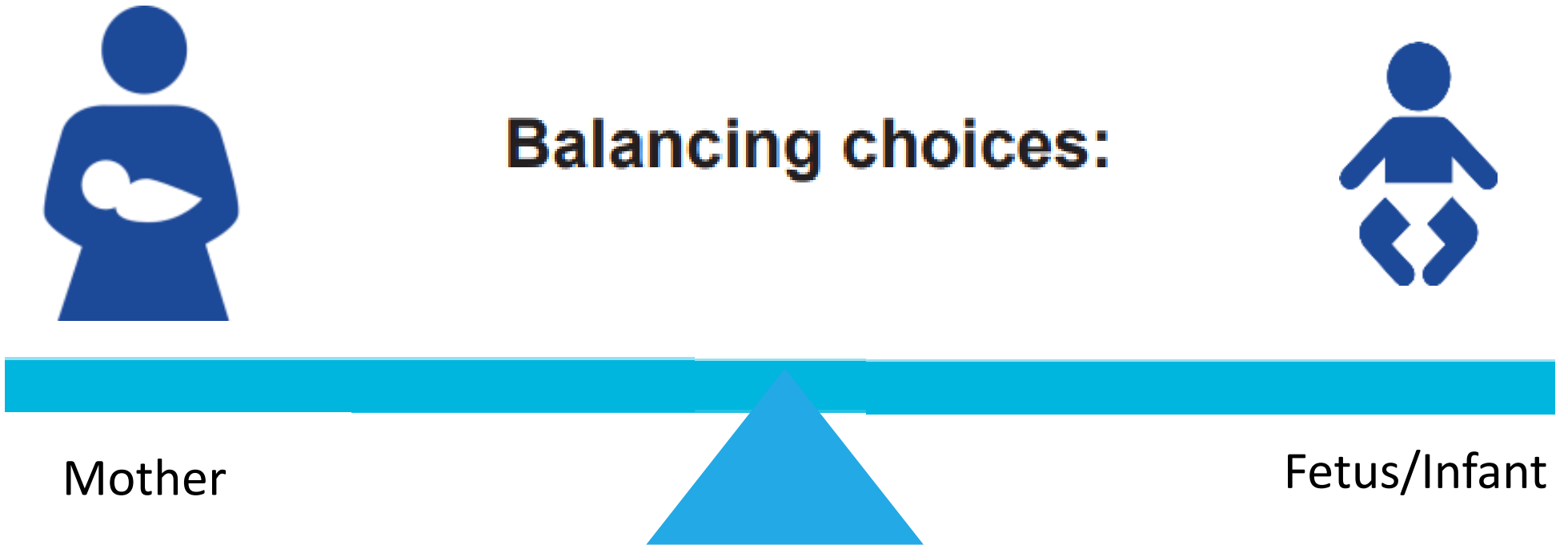


Case study 1 - Daniella

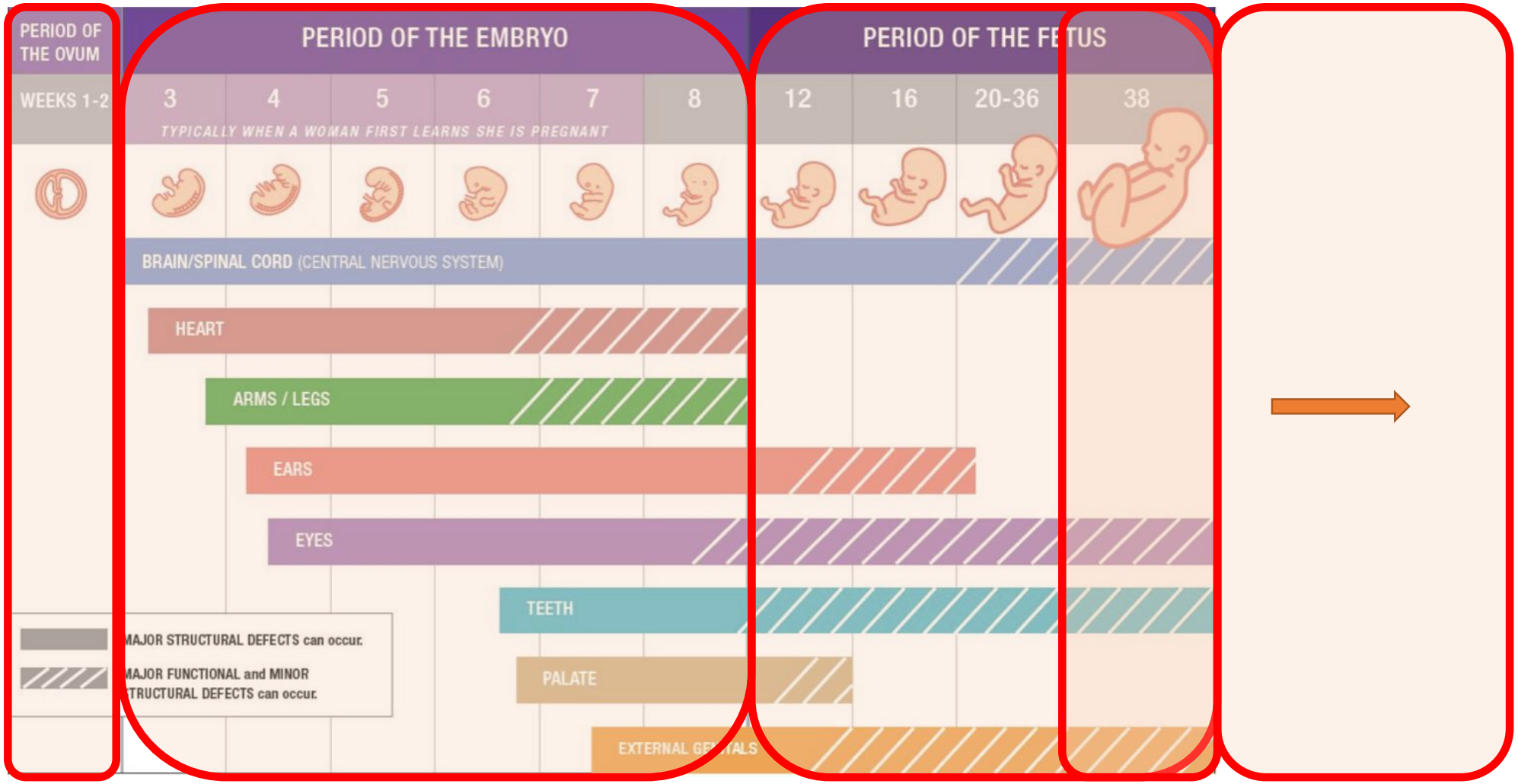
- 35 Years, G3P1, 28/40
- Rheumatoid arthritis – Current flare
- Meds:
  - Aspirin 150mg OD
  - Folic acid 400 micrograms
  - Tinzaparin 4500 units OD
  - Prednisolone 20mg OD
  - Previously on etanercept, methotrexate
- Team prescribed certolizumab, but patient hesitant.

What to consider…

1. The stage of pregnancy
2. The maternal condition
3. Potential for fetal/neonatal risks from medication exposure
   - Degree of systemic exposure and transfer across the placenta
   - Mechanism and effects of the drug
   - Dose, Duration and Polytherapy
4. Quality of evidence of fetal/neonatal risks
5. Quality of the evidence
6. Patient preference and values

What to consider…

1. The stage of pregnancy



What to consider…

1. The stage of pregnancy
2. **The maternal condition**
   - Severity and stability
   - Benefits of treatment
   - Consequences of no treatment or under treatment
   - Alternative approaches

What to consider…

1. The stage of pregnancy
2. The maternal condition
3. **Potential for fetal/neonatal risks from medication exposure**
   - Degree of systemic exposure
   - Transfer across the placenta
   - Mechanism and effects of the drug (e.g. Teratogenic effect, Pharmacological effect, Other)
   - Dose and Duration – Dose-dependent teratogenicity
   - Polytherapy

What to consider…

1. The stage of pregnancy
2. The maternal condition
3. Potential for fetal/neonatal risks from medication exposure
4. **Evidence of fetal/neonatal risks**
   - Spontaneous abortion / miscarriage (Background risk: 10-20%)
   - Congenital malformation (Background risk: 2-3%)
   - Intrauterine growth restriction (IUGR)
   - Intrauterine death
   - Pre-term birth
   - Neonatal complications / disorders
   - Neurodevelopmental disorders (Background risk: 2-8%)

What to consider…

1. The stage of pregnancy
2. The maternal condition
3. Potential for fetal/neonatal risks from medication exposure
4. Evidence of fetal/neonatal risks
5. **Quality of evidence**

What to consider…

1. The stage of pregnancy
2. The maternal condition
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5. Quality of evidence
6. **Patient Preference and values**

What to consider…

1. **The stage of pregnancy**
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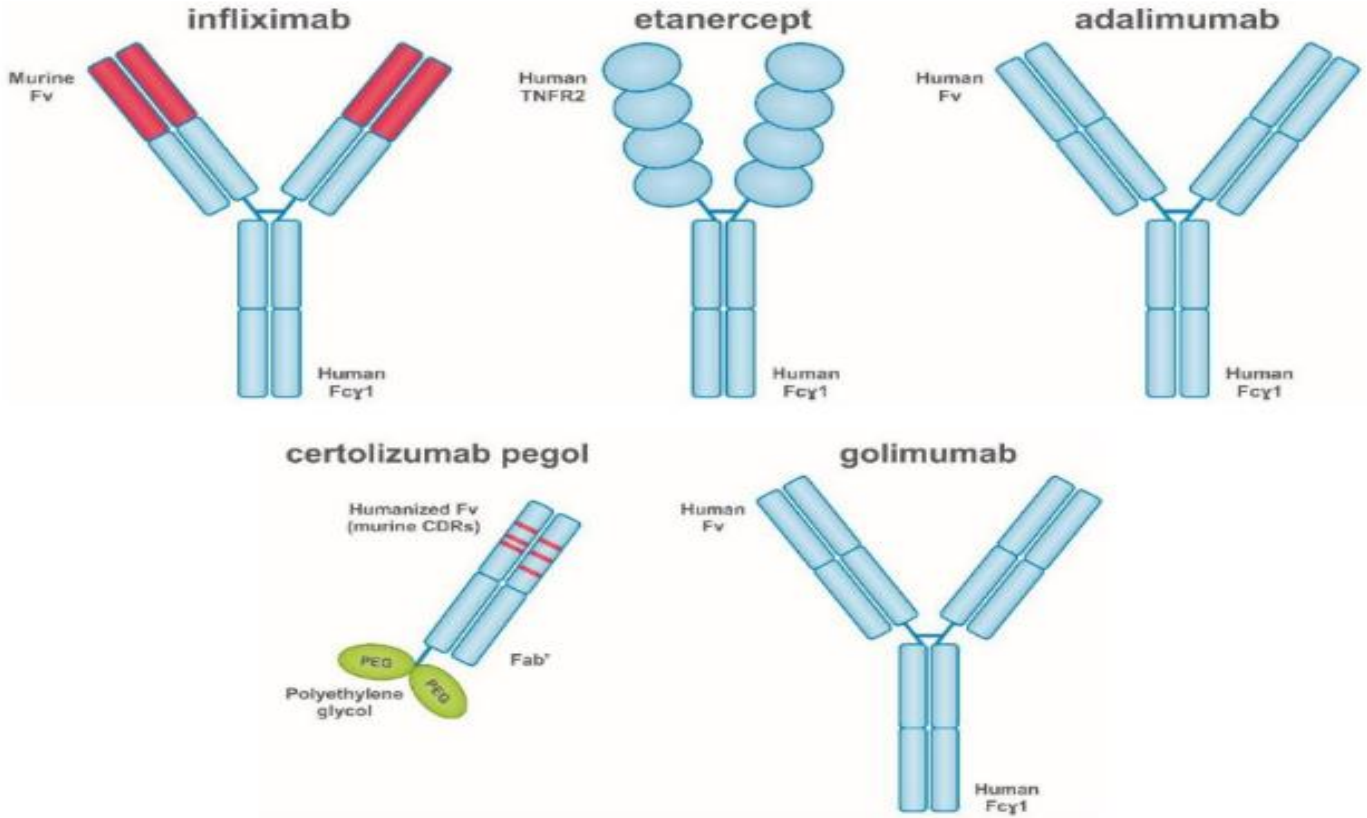

Case study 1 - Daniella

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Pregnancy

Human data

A large amount of data (more than 1500 pregnancies exposed to Cimzia during the first trimester) from prospectively reported pregnancies with known pregnancy outcomes, indicate no malformative nor feto/neonatal toxicity. Continuous data collection is ongoing with pharmacovigilance cases reporting and a pregnancy registry.

certolizumab pegol golimumab

section 5.2).

In a clinical study 16 women were treated with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 µg/ml with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last Cimzia administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.

Evaluating information

What information is available?

1. Animal studies
2. Case reports/Case series
3. Case control studies
4. Cohort studies/Database studies
5. Systematic reviews and Meta analyses

Critically Appraising the Evidence

- Who was studied?
- What is the comparator?
- What is being measured?
- Is the timing of exposure defined?
- Is the data fit for purpose?
- Consider potential bias (e.g. Confounding by indication, Selection, Misclassification)
- Are findings consistent?
- How does this apply to my patient?

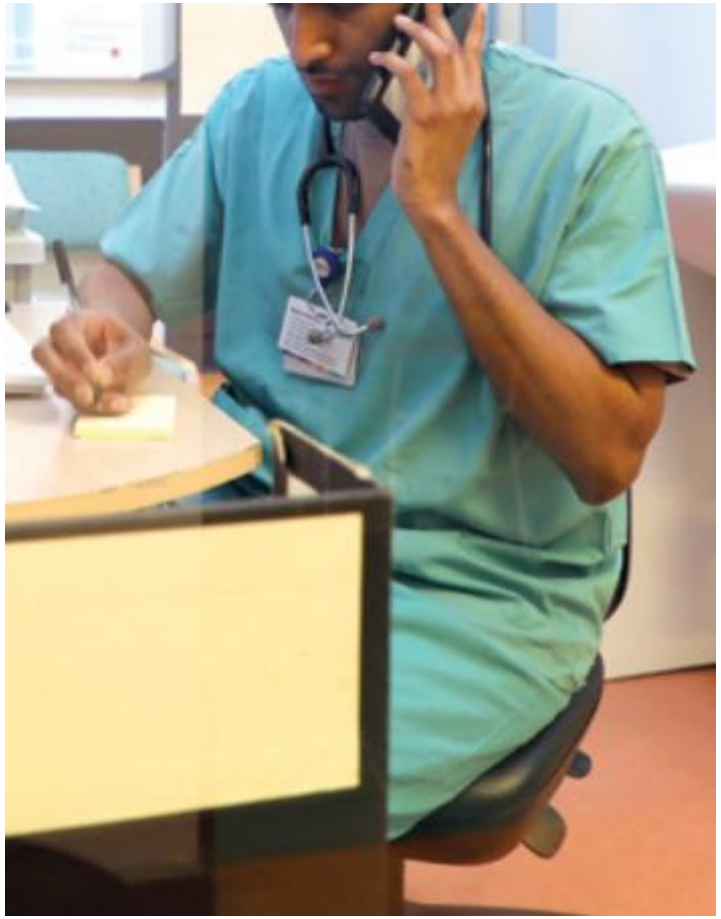
Critically Appraising the Evidence

- Data from multiple sources
- Biological plausibility
- High quality data quality
- Robust study methodology
- Consistency in results

- Results based on small numbers
- No appropriate comparator
- Conclusions stronger than data supports
- Relative risk reported without absolute risk
- Findings are inconsistent across studies

Case study 2

- Dr Abdul, GP
- Patient attends ~6 weeks' gestation
- Current Depression- managed with Paroxetine 20mg OD
- Hx of Postnatal Depression and Suicidal Ideation
- Patient has concerns about cardiac defects



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Mental Health Conditions in Pregnancy

- Stopping antidepressants during or prior to pregnancy may lead to worse maternal depression, which is a known risk factor for serious adverse pregnancy outcomes.
- Suicide is the leading cause of maternal death occurring between 6 weeks – 12 months postpartum
- Deaths from psychiatric causes accounted for 33% of maternal deaths overall.

SSRI Timeline

- Pre-2005- safety data reassuring
- 2005 FDA Public Health Advisory on paroxetine and cardiac septal defects:
    - Swedish Medical Birth Register
    - US insurance claims database
- Confirmed in subsequent studies
- 2010 EMEA- similar warning for fluoxetine

BMJ open
accessible medical research

To cite: Jimenez-Solem E, Andersen JT, Petersen M, *et al*. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. *BMJ Open* 2012;**2**:e001148. doi:10.1136/bmjopen-2012-001148

Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study

Espen Jimenez-Solem,[1,2] Jon Traerup Andersen,[1,2] Morten Petersen,[1,2]

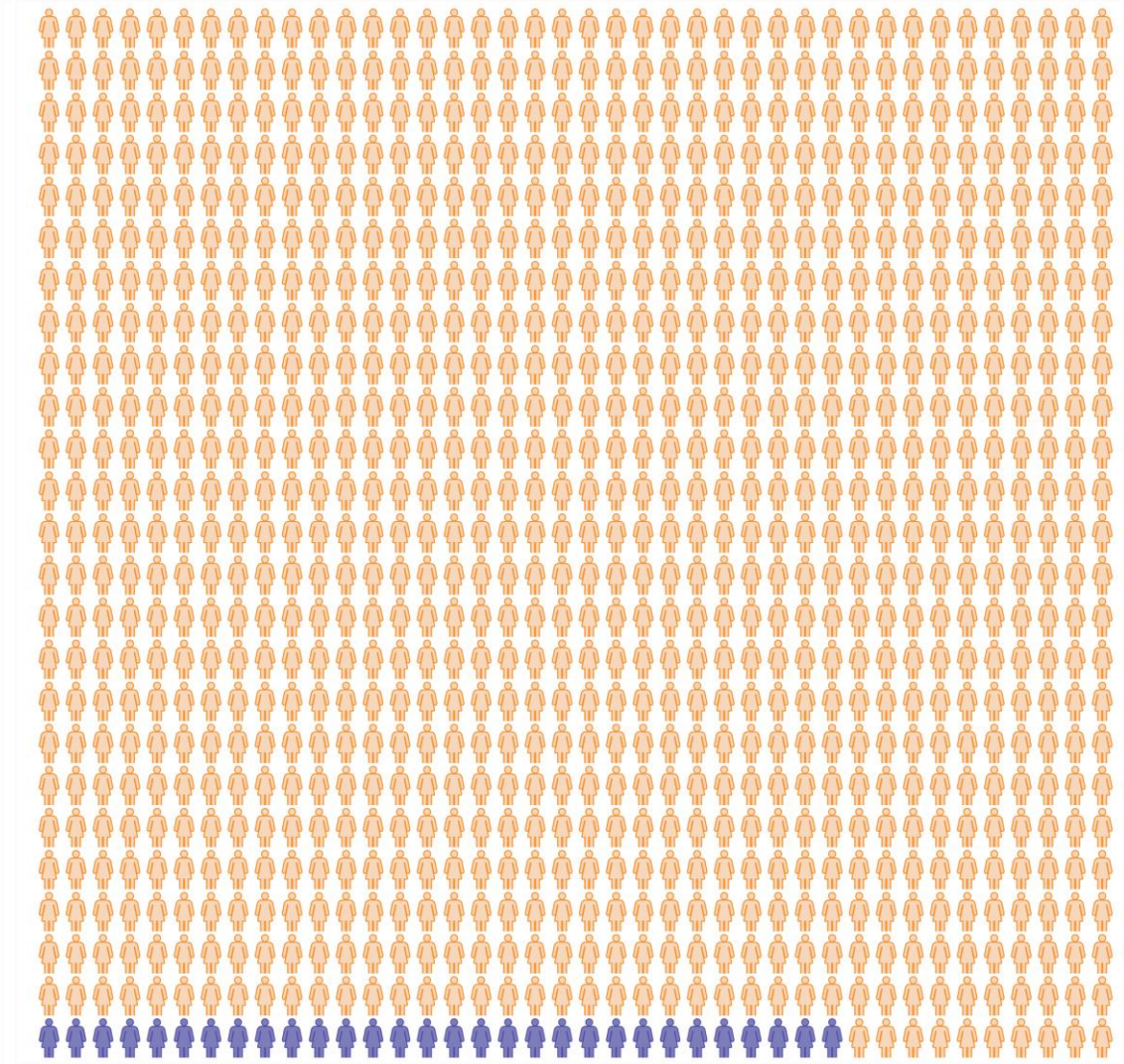
Table 2 Risk of congenital malformations among women exposed to an SSRI versus women with no exposure

	Exposed to any SSRI					
	First trimester (n=4183)		Paused during pregnancy (n=806)			No exposure (n=843 797)
Outcome	n (%)	OR (95% CI)†	n (%)	OR (95% CI)†	p Value*	n (%)
Major malformations	208 (4.97)	1.33 (1.16 to 1.53)	36 (4.47)	1.27 (0.91 to 1.78)	0.90	29 703 (3.52)
Congenital malformations of the heart	77 (1.84)	2.01 (1.60 to 2.53)	13 (1.61)	1.85 (1.07 to 3.20)	0.94	7755 (0.92)
Septal defects	49 (1.17)	2.04 (1.53 to 2.72)	11 (1.36)	2.56 (1.41 to 4.64)	0.35	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.62 (1.05 to 2.50)	9 (1.12)	3.74 (1.93 to 7.23)	0.97	2803 (0.33)
Atrial septal defects	34 (0.81)	2.60 (1.84 to 3.68)	6 (0.74)	2.61 (1.17 to 5.84)	0.74	2490 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.80 (1.04 to 3.12)	1 (0.12)	0.75 (0.11 to 5.35)	0.59	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.84 (0.45 to 1.57)	–	–	–	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.55 (0.99 to 2.44)	2 (0.25)	0.89 (0.22 to 3.59)	0.46	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71 to 1.23)	14 (1.74)	1.37 (0.80 to 2.32)	0.18	11 785 (1.40)

Estimates are presented as ORs with 95% CIs.
*p Value for comparison of ORs between pregnancies exposed throughout the first trimester and pregnancies with paused exposure during pregnancy.
†Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.
SSRI, selective serotonin reuptake inhibitor.

1

Background rate

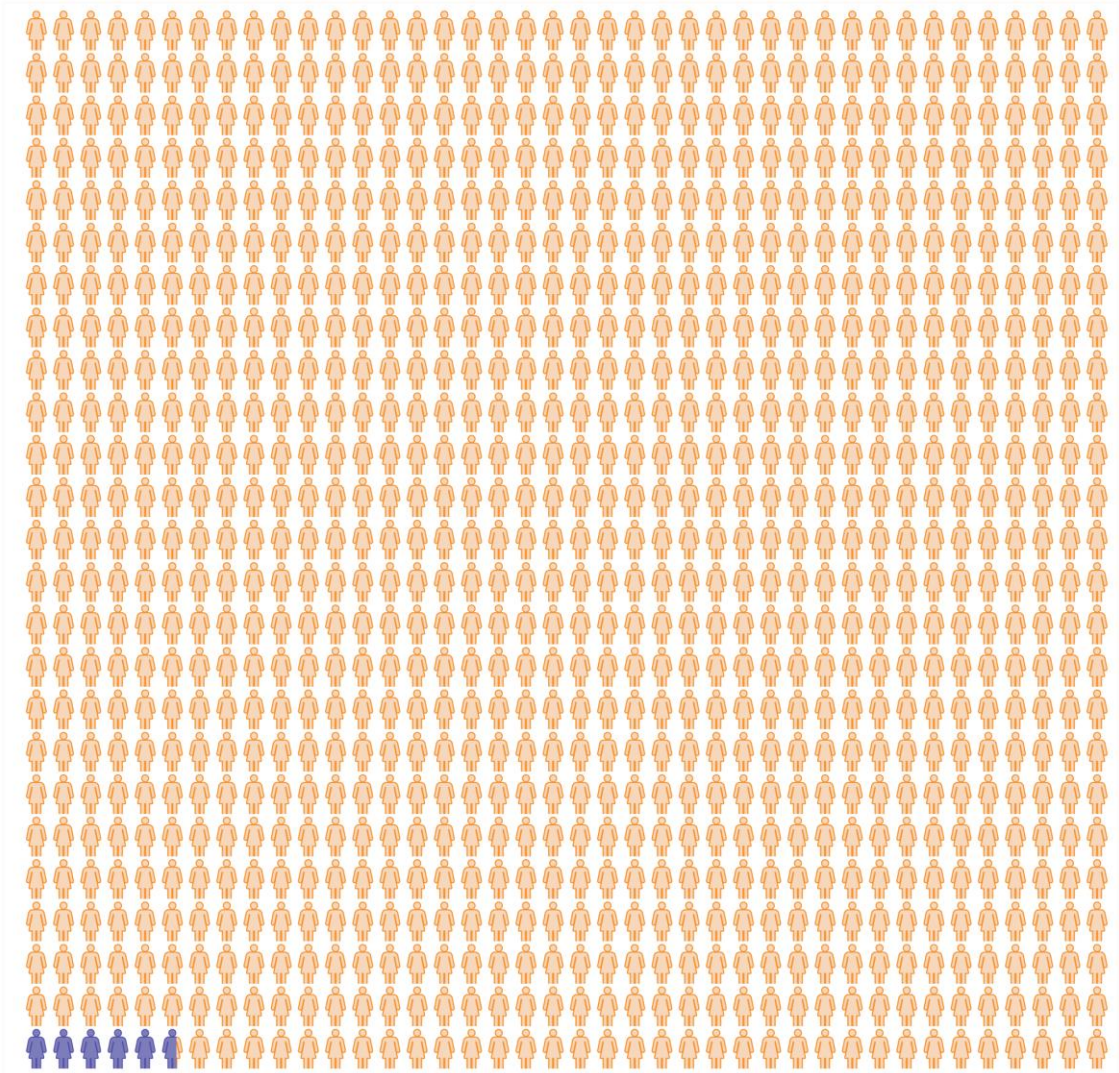


3% of all pregnant women will have a baby born with a birth defect. This is called the **background rate**

Reference: Jimenez-Solem et al., 2012

2

Cardiac septal defects – No SSRI

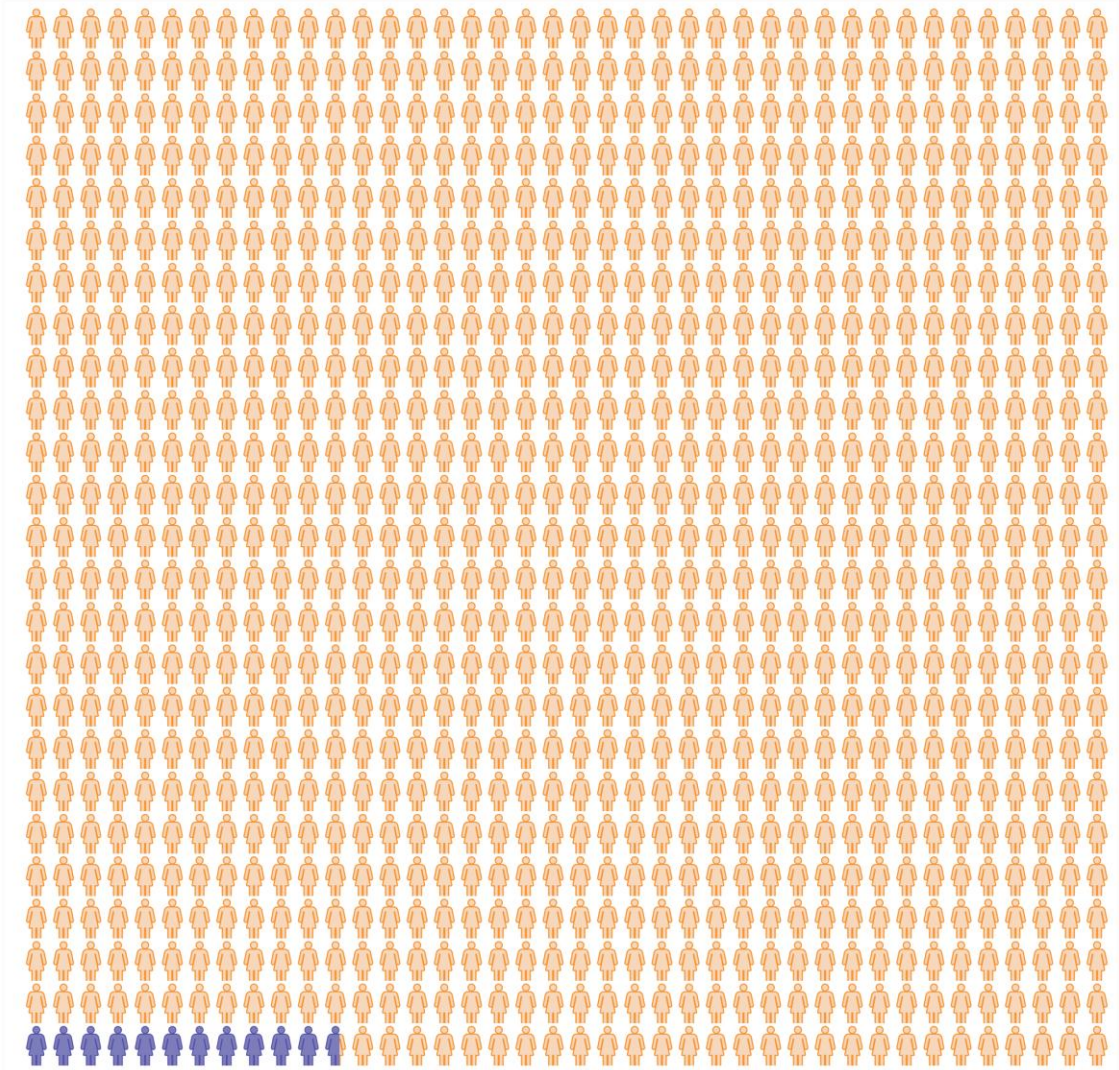


0.57% of pregnant women who were **not taking** an SSRI antidepressant had a baby with a cardiac septal defect

Reference: Jimenez-Solem et al., 2012

3

Cardiac septal defects – SSRI in first trimester

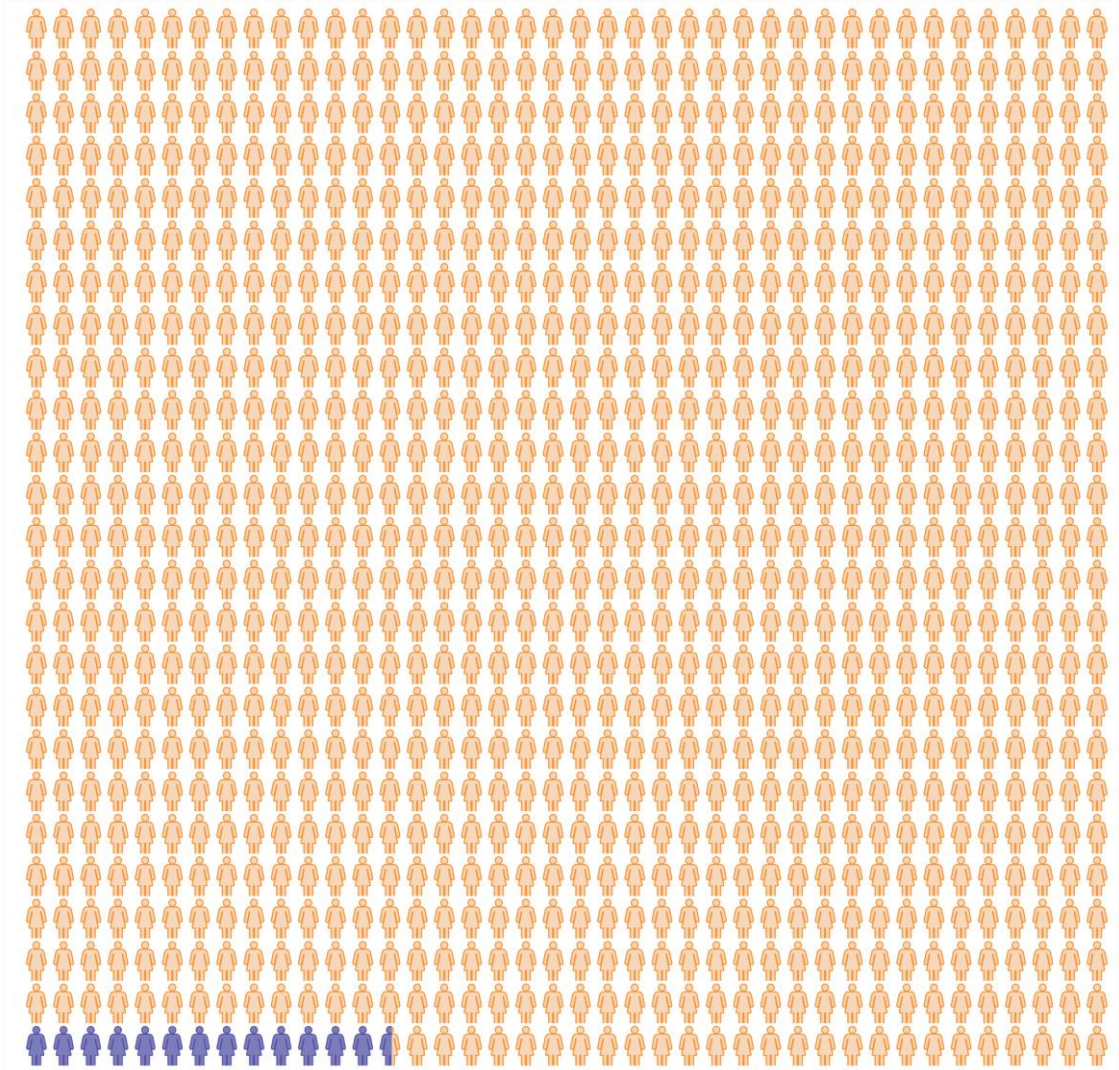


1.17% of pregnant women who **were taking** an SSRI antidepressant had a baby with a cardiac septal defect

Reference: Jimenez-Solem et al., 2012

4

Cardiac septal defects – SSRI paused



1.36% of pregnant women who **paused** an SSRI antidepressant had a baby with a cardiac septal defect

Reference: Jimenez-Solem et al., 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

Krista F. Huybrechts, Ph.D., Kristin Palmsten, Sc.D., Jerry Avorn, M.D., Lee S. Cohen, M.D., Lewis B. Holmes, M.D., Jessica M. Franklin, Ph.D., Helen Mogun, M.S., Raisa Levin, M.S., Mary Kowal, B.A., Soko Setoguchi, M.D., Dr.P.H., and Sonia Hernández-Díaz, M.D., Dr.P.H.

Overall Cohort

SSRI	No Exposure
(N=46,144)	(N=885,115)

Depression-Restricted Cohort†

SSRI	No Exposure
(N=36,778)	(N=180,564)

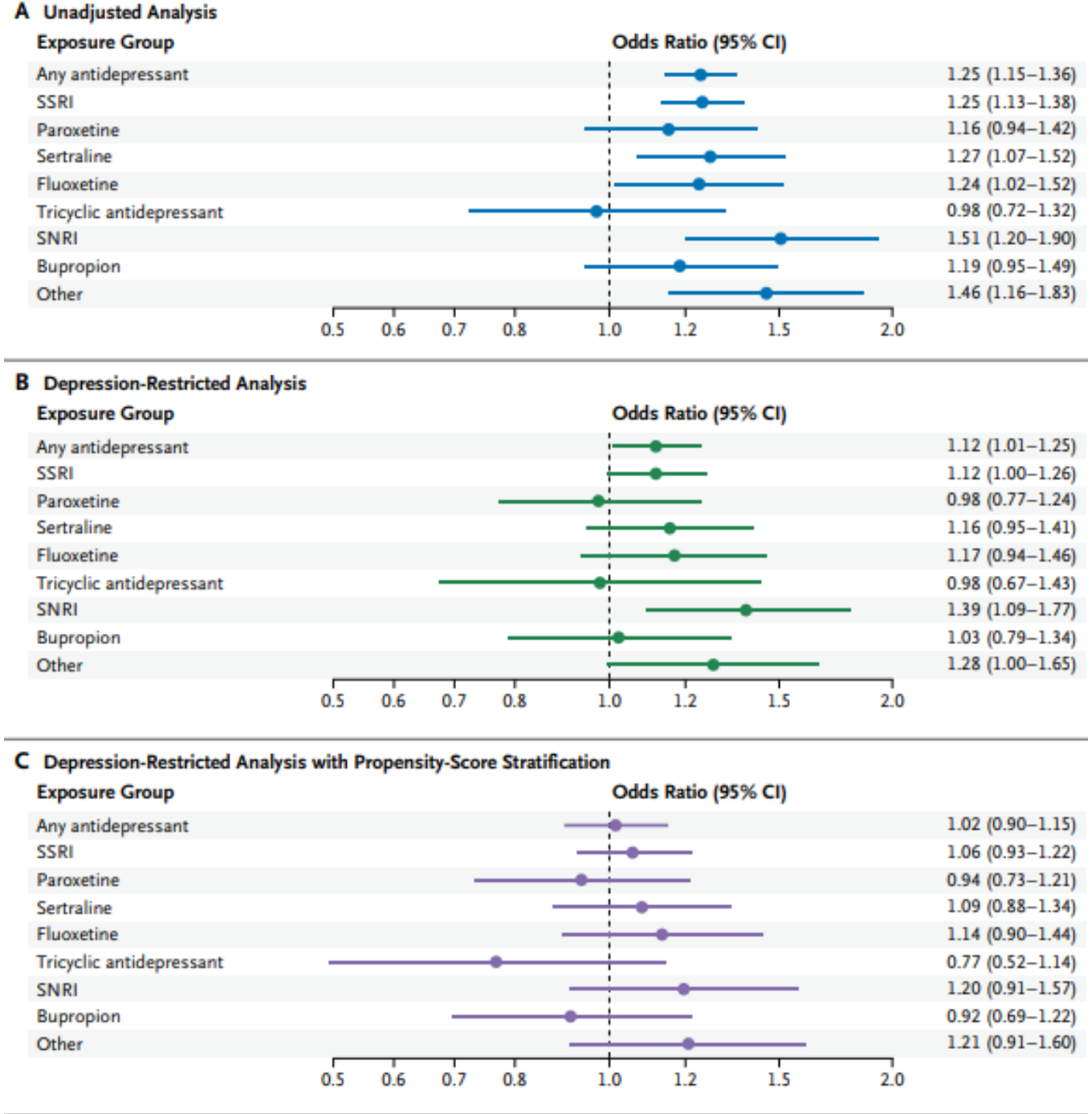


Figure 1. Risk of Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

Cardiac Septal Defects

- Animal & human data suggest role for serotonin in cardiac development
- Paroxetine/fluoxetine association consistent across earlier studies
- Limited/inconsistent data for other SSRIs
- May be a class effect
- False association/potential confounding by indication?

Case study 2

- Dr Abdul, GP
- Patient attends ~6 weeks' gestation
- Current Depression- managed with Paroxetine 20mg OD
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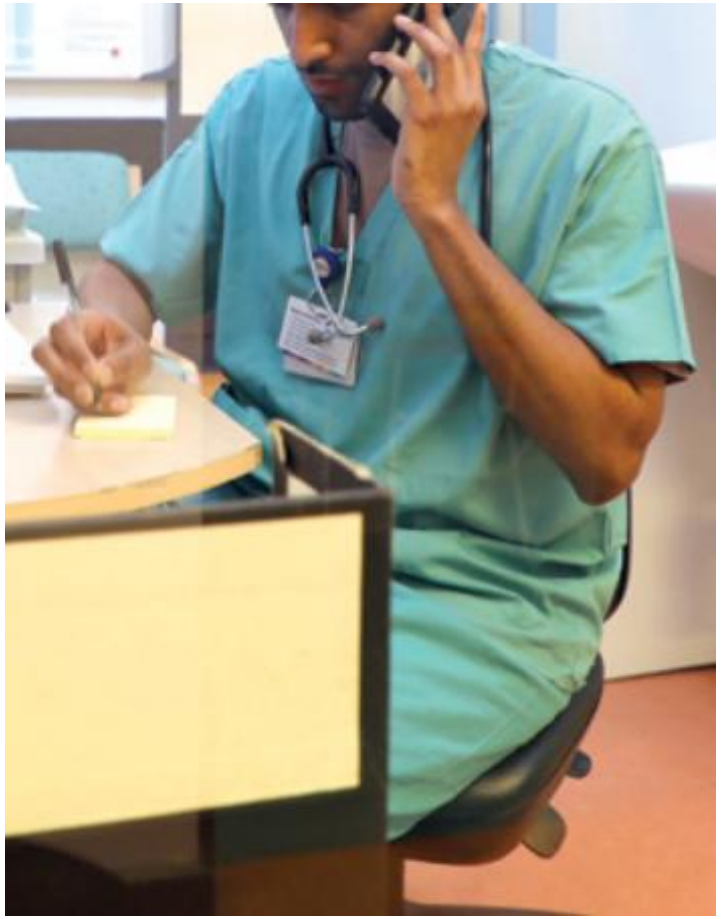


Medication use in breastfeeding

How medicines get into breastmilk…

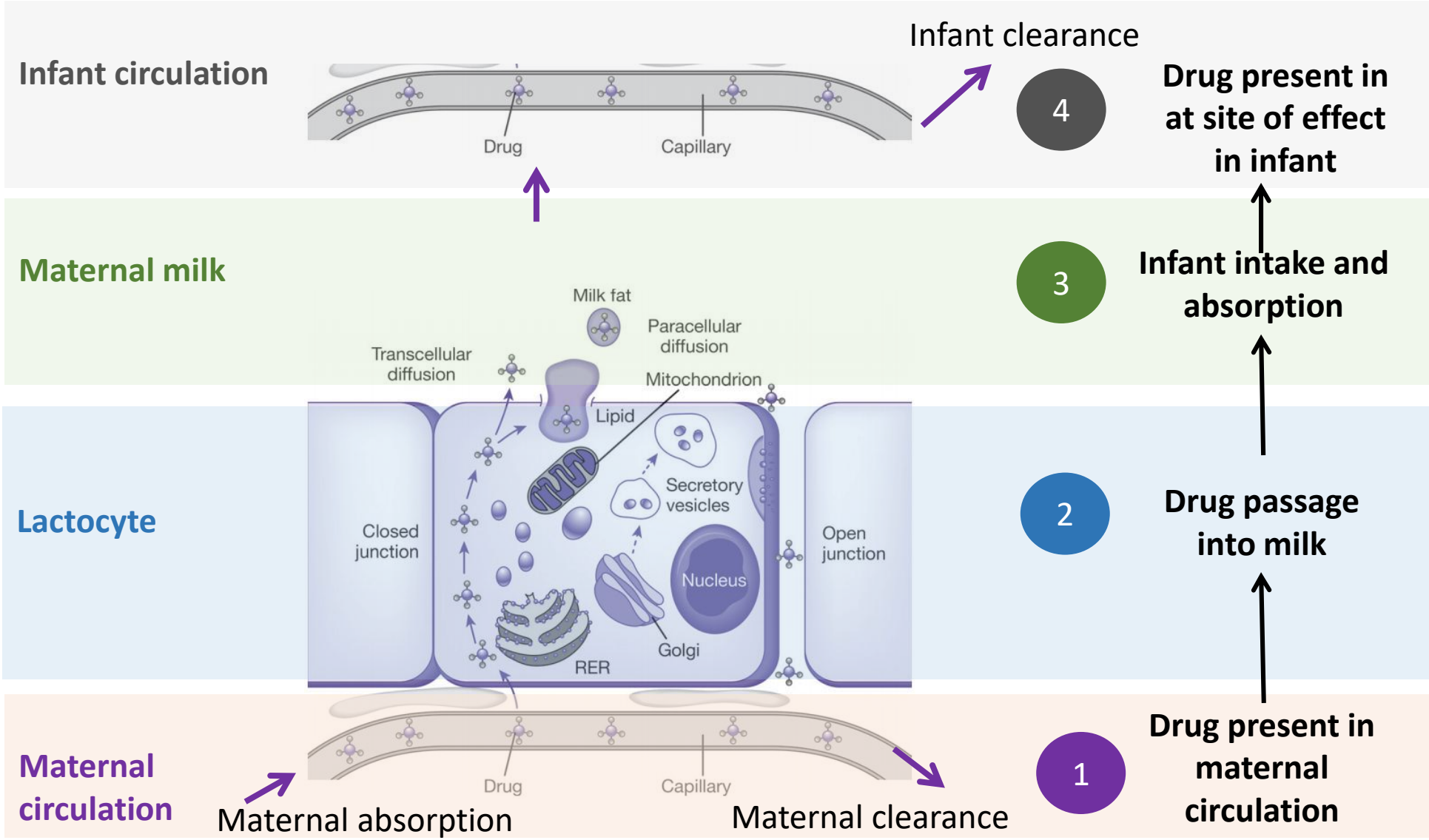
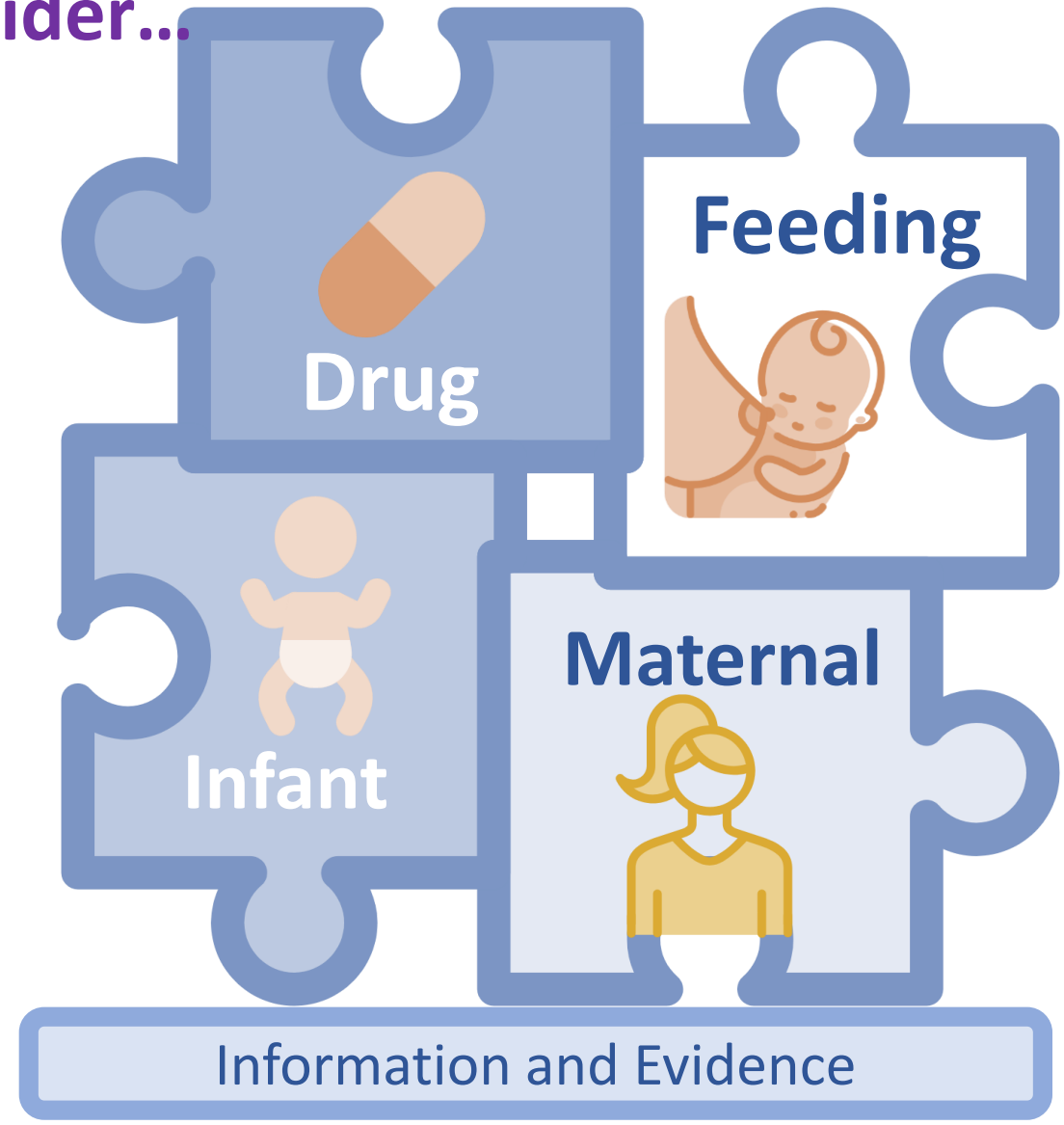


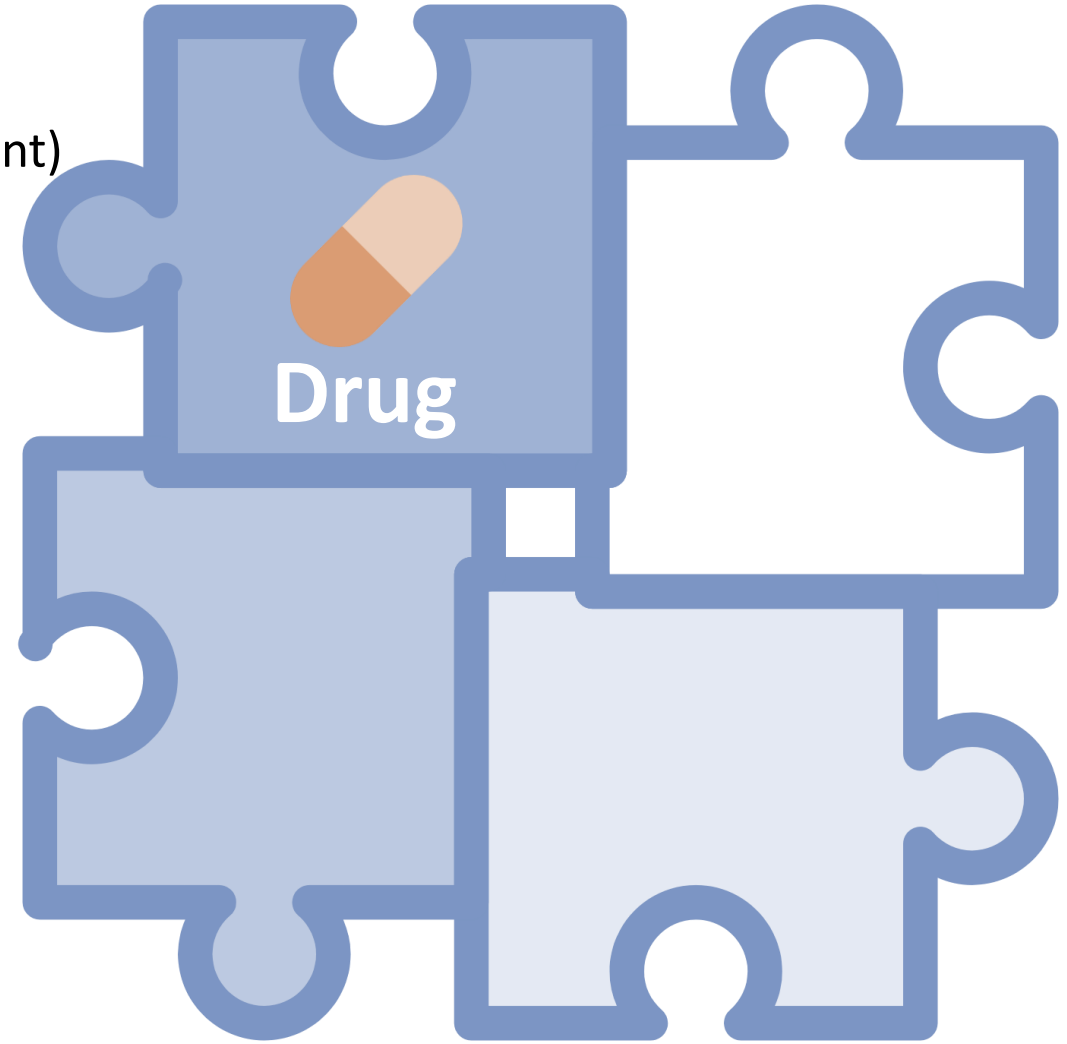
Image from Halemeds.com

Factors to consider…



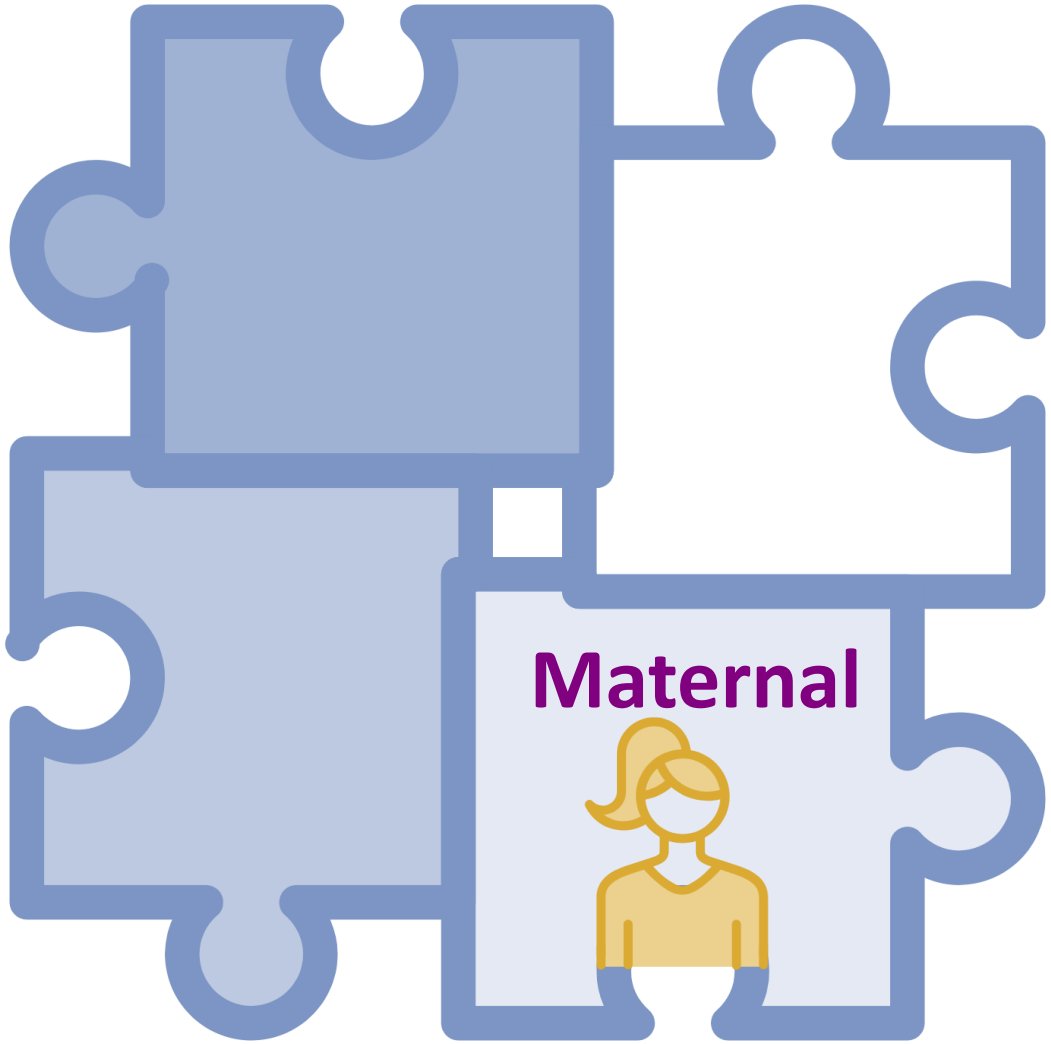
Factors to consider…

- Oral bioavailability
- Metabolism and elimination (Maternal and infant)
- Half life
- Volume of distribution
- Milk/Plasma ratio
- Protein Binding
- Tmax
- pKa
- Molecular weight
- Lipid solubility
- Relative infant dose (RID)



Factors to consider…

- **Drug therapy:**
  - Drug
  - Dose
  - Route
  - Formulation (immediate vs. prolonged)
  - Intended duration
- **Maternal health**
  - Renal function
  - Hepatic function
- **Genetic** differences in metabolism e.g. Codeine

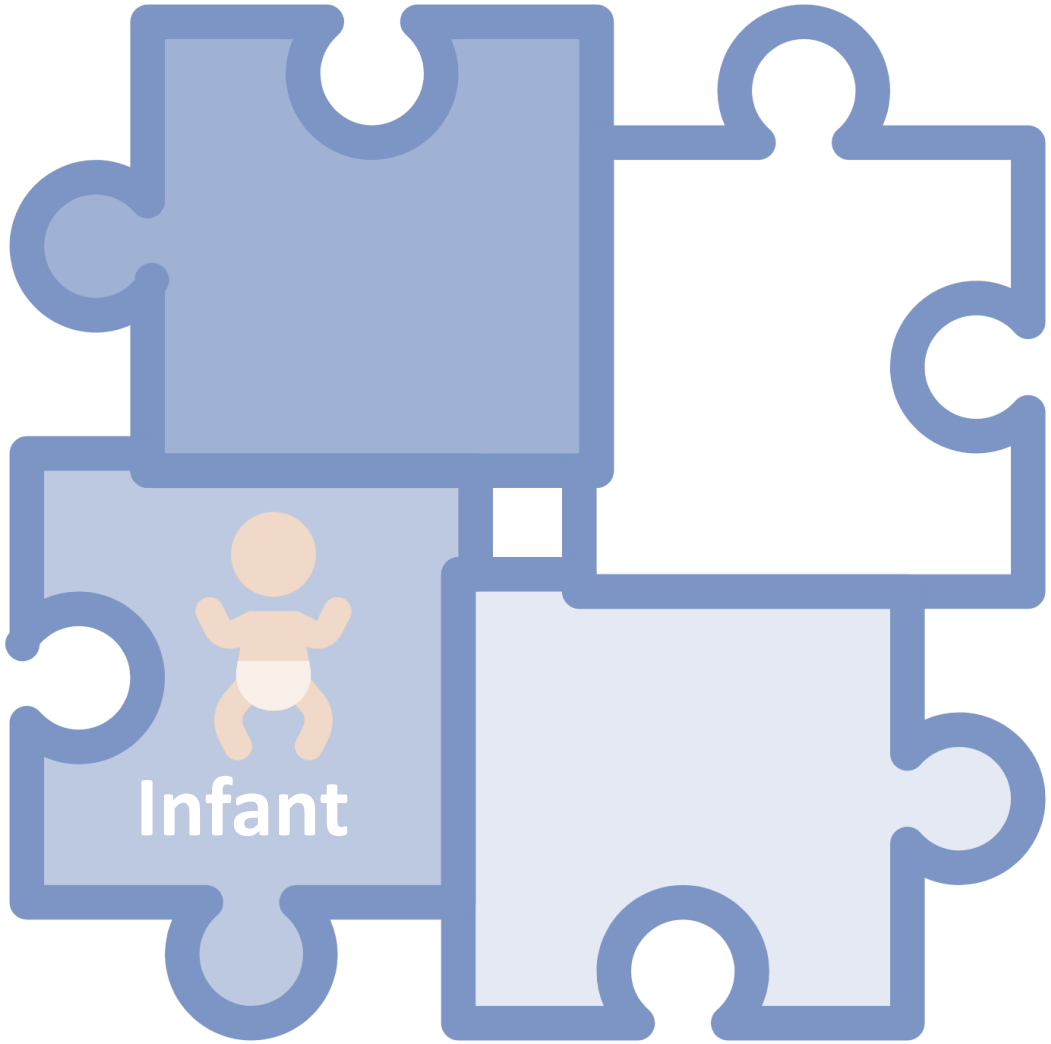


Factors to consider…

- **Stage of lactation**
  - Colostrum
  - Mature milk – foremilk vs. hind milk
  - Longer term feeding
- **Exclusively breast fed? Combined feeding?**
- **Feeding frequency**

Factors to consider…

- **Gestational age at delivery**
  - Premature & newborn infants → Caution
    - Immature renal and hepatic systems → Immature blood brain barrier
    - Changes in protein binding
- **Current age**
  - Older infants may be at lower risk due to high metabolic capacity and lower feeding frequency
- **Health of the infant**
  - Concurrent or underlying health conditions
  - Renal or hepatic dysfunction



IMPS approach to medicines and breastfeeding

- Breast feeding should be **promoted and facilitated** as much as possible
- Consider on a **case by case** basis
- Start with a 

and try to find strong rationale against this
- Individualised **risk-benefit decision** → Consider both infant and mother
- Medication **should not be withheld** on account of breastfeeding/safety concerns/theoretical concerns
- A recommendation to stop breastfeeding or advising against a medication in breastfeeding not be made lightly
- Provide information to **support and empower informed decisions**. Provide reassurance and encouragement

IMPS approach to medicines and breastfeeding

- Avoid unnecessary medicines. Consider alternatives: Non-pharmacological? Alternative route? Alternative agent?
- Choose a drug with published data
- Choose drugs that pass poorly into milk and have no active metabolites
  - Low oral bioavailability
  - High MW
  - High Protein binding
  - Short half lives
  - Low M/P
  - Low RID
- **Monotherapy** is preferable. Use the **lowest effective dose** for the **shortest duration** possible. Avoid long acting formulations
- Low volume of milk in the first 3 – 4 days limit potential exposure
- **Caution with preterm infants or neonates**. Potential risks lower with older infants
- Monitor the infant where appropriate. Advice on co-sleeping/bed sharing

Risk Communication and Shared Decision Making

What is risk?

- From a statistical perspective, risk is neutral and numerical
- From a patient perspective, risk is a feeling which is subject to individual interpretations and influenced by personal characteristics, values and context
- Communicating the concepts and details of risk in an accurate and understandable way can be challenging

Adapted from SMFM. Consult Series# 55: Counseling women at increased risk of maternal morbidity and mortality. AJOG. 2021

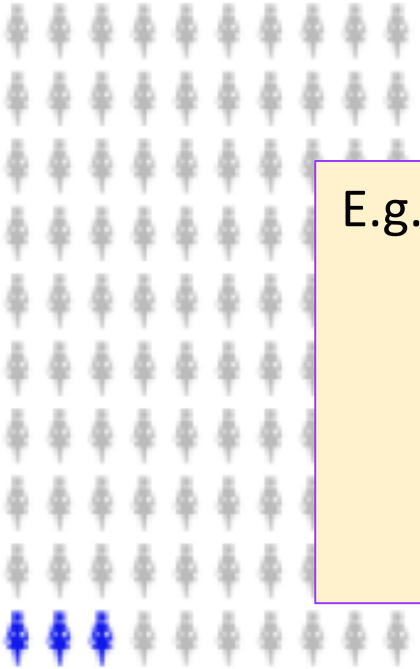
General approach to communicating risks/benefits

- Clearly describe the risk and who it applies to e.g. Animals data vs. human experience.
- Use plain language and explain in terms that the patient will understand
- Pay attention to the description and format of numbers
  - Avoid replacing numbers with words → Avoid low risk, high risk etc.
  - Distinguish between relative and absolute risks
  - Use consistent denominators when comparing risk → (e.g. 4/1000 vs. 20/1000)
- Use balanced framing → Positive and negative outcomes
- Use visual aids and infographics
- Give balanced information
- Explain uncertainties
- Consider other and competing risks e.g. baseline risk, other treatment, no treatment.

Adapted from SMFM. Consult Series# 55: Counseling women at increased risk of maternal morbidity and mortality. AJOG. 2021

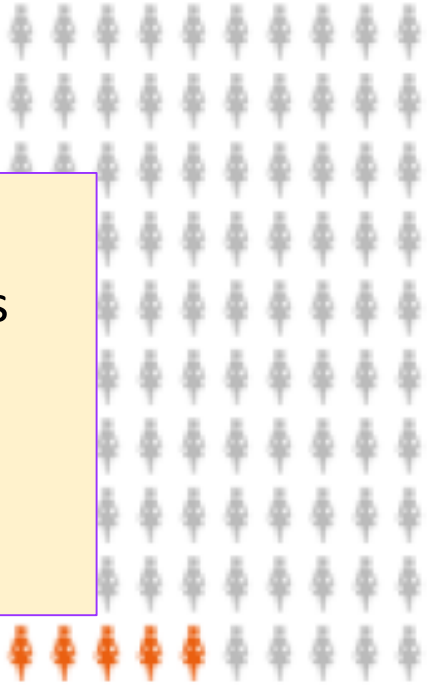
Example of risk communication approaches - Carbamazepine

If 100 women give birth in the general population, 2 or 3 will have a baby born with a congenital abnormality.



This is called the background rate

If 100 women take carbamazepine in pregnancy, 4 or 5 of their babies will be born with a congenital abnormality.



This is higher than the background rate but the overall risk is low

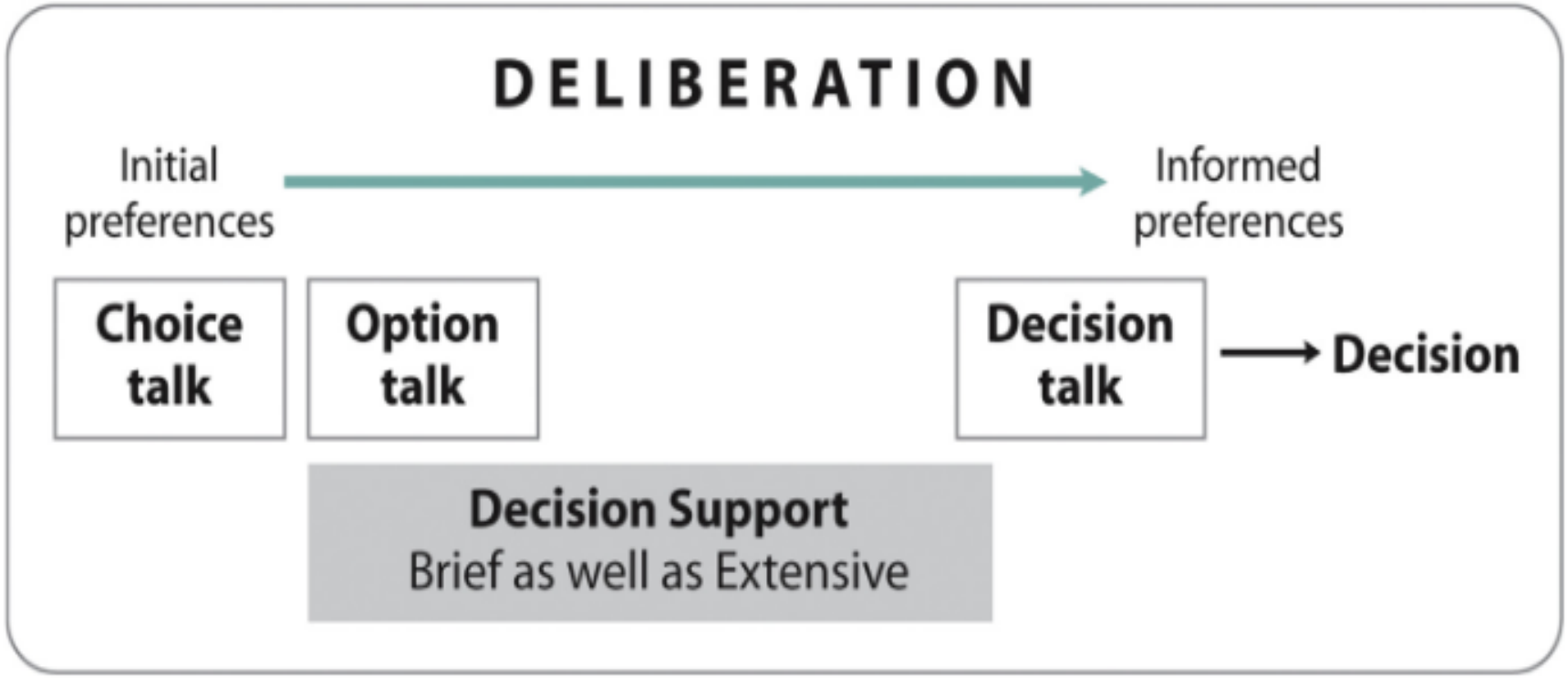
E.g. of communication techniques

1. Consistent denominators
2. Balanced framing
3. Absolute risk estimates
4. Infographics

Communicating uncertainties or information gaps

- Explain what is known
- Explain what is unknown / information gaps
- Describing limits of knowledge and outcomes with less data e.g. long term neurodevelopmental outcomes
- Address conflicting findings
- Communicating the best summary/current scientific consensus
- Give appropriate caveats on available information, (also on benefits/harms of doing nothing)

Shared decision making model



SMFM. Consult Series# 55: Counselling women at increased risk of maternal morbidity and mortality. AJOG. 2021

Factors Influencing Decisions

- Previous pregnancy experience
- Personal/family experiences
- Risk perception
- Health literacy
- Cultural factors

Where to get information - Pregnancy

UKTIS

uktis
uk teratology information service

BUMPS & Mother To Baby

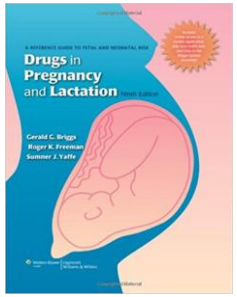
Bumps

MotherToBaby®

UpToDate Lexidrug

Australian Medicines Handbook

Drugs in pregnancy and Lactation, Briggs



LeCrat.fr

CRAT

www.embryotox.de

Reprotox

REPROTOX®

Local and Specialist MI services

IMPS
Irish Medicines in Pregnancy Service

NATIONAL MEDICINES INFORMATION CENTRE

Where to get information - Breastfeeding

Lactmed

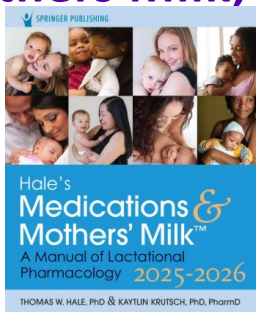
E-Lactancia

e-lactancia

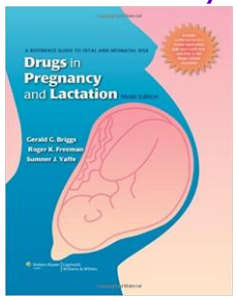
NHS Medicines A-Z

NHS

Medications and Mothers Milk, Hale



Drugs in pregnancy and Lactation, Briggs



SmPC

HPRA

BNF

SPS

Specialist Pharmacy Service

BFN

the Breastfeeding network

Local and specialist MI services

IMPS
Irish Medicines in Pregnancy Service

NATIONAL MEDICINES INFORMATION CENTRE

UKDILAS
UK Drugs in Lactation Advisory Service

Where are patients getting their information?

Support groups or online communities

Social media/ influencers

Internet searches / Fora

Peers, friends, family

Healthcare professionals

Thank you

Irish Medicines in Pregnancy Service
Rotunda Hospital
Dublin
Bcleary@Rotunda.ie
NMaher@Rotunda.ie
MedicinesInPregnancy@Rotunda.ie