Teratogenicity And Malformations In Pregnancy Secondary To Psychotropic Drugs

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Outline

- The perinatal period
- The clinical problem
- Risk periods for foetal structural malformations.
- FDA drug catagories.
- Classes of psychotropics

The Perinatal Period

- A uniquely stressful time.
- Pre-existing psychological conditions can be exacerbated by the stresses of the period.
- Many psychological illnesses have an increased risk of onset at this time.
- Whether some psychological illnesses occur uniquely in this period is controversial.

The Clinical Problem

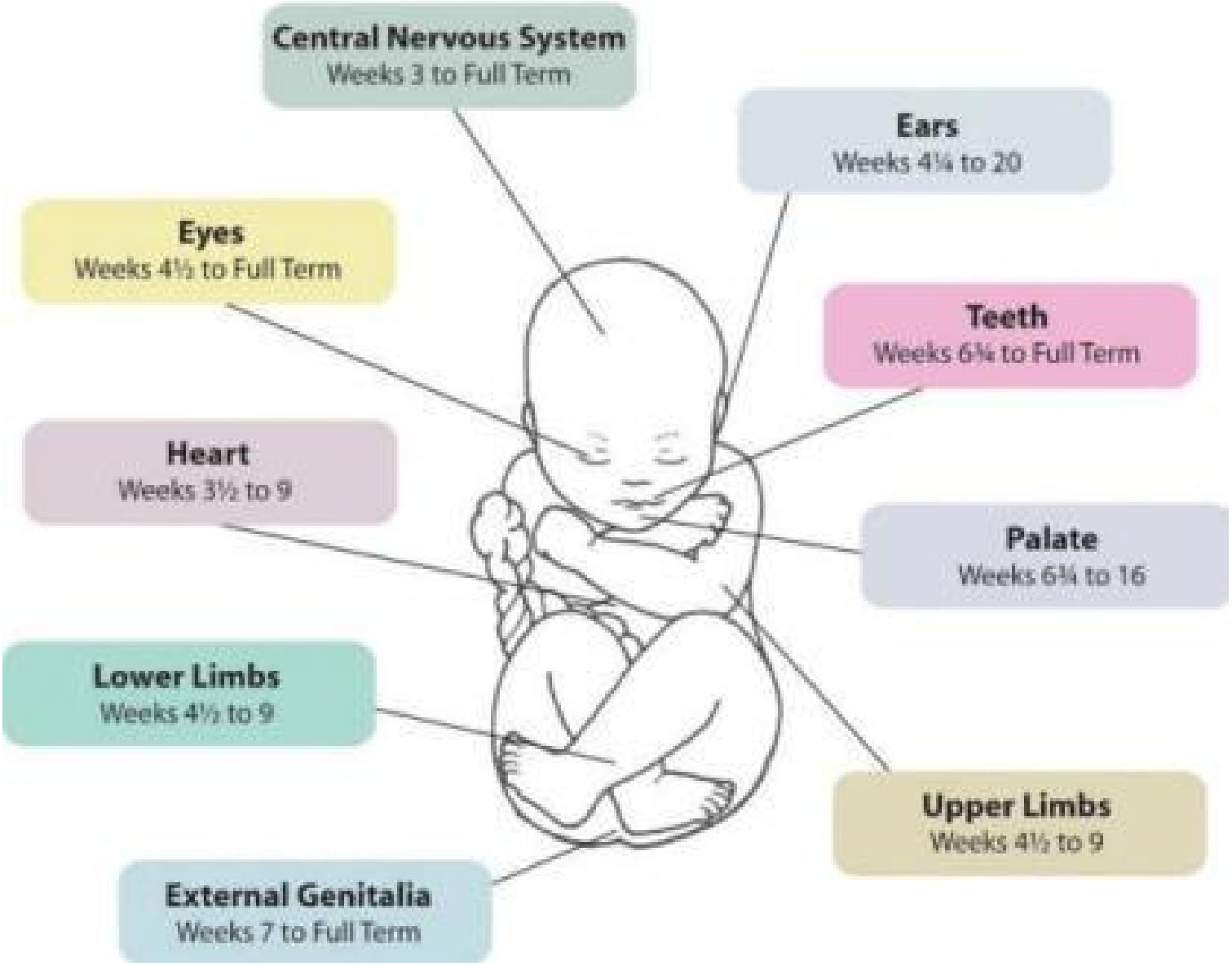
Defining Exposure

There are 2 exposures

1. What will the foetus/baby be exposed to in terms of medication?

2. What will the foetus/baby be exposed to in terms of maternal psychiatric illness?

Maternal Depression and Medication Exposure During Pregnancy : Comparison of Maternal Retrospective Recall to Prospective Documentation DJ Newport, PA Brennan, […], and ZN Stowe


Central Nervous System
Weeks 3 to Full Term
Ears
Weeks 4¼ to 20
Eyes
Weeks 4½ to Full Term
Teeth
Weeks 6¼ to Full Term
Heart
Weeks 3½ to 9
Palate
Weeks 6¼ to 16
Lower Limbs
Weeks 4½ to 9
Upper Limbs
Weeks 4½ to 9
External Genitalia
Weeks 7 to Full Term

Risk Periods for Foetal Structural Malformations.

- 2-4 weeks neural tube closure
- 4-9 weeks heart is forming
- 6-9 weeks is when the oral cleft closes
- by 12 weeks organogenesis is completed

Two Basic Assumptions.

1. All medications cross the placenta.

2. We do not yet know all the potential risks from medication exposure.

- For every patient Risks of treatment vs the benefits of treatment.
- or *risks of treatment* vs *risks of non-treatment should be evaluated*

FDA: “Use in Pregnancy”- Drug categories.

- Category A: Controlled studies show no risk.
- Category B: No evidence of risk in humans
- Category C: Risk to humans cannot be ruled out
- Category D: Positive evidence of risk but it is possible in some situations the benefits may outweigh the risks
- Category X: Contraindicated in pregnancy. Risks outweigh the benefits in almost every situation.

Classes of psychotropics

- Antidepressants and Anxiolytics
  - SSRI's
  - Tricyclics
  - Benzodiazepine
- Mood Stabilisers and anticonvulsant
  - Valproate
  - Lithium
  - Carbamazepine
  - Lamotrigine
- Antipsychotics
  - First generation
  - Second generation

Tricyclic Antidepressants

- Low incidence of perinatal syndromes.
- The data is reassuring .
- Nulman (2002). No negative behavioural sequelae up to 6 years.

Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life : a prospective, controlled study by Nulman I, et al. Am J Psychiatry. 2002.

SSRI'S

Fluoxetine

- Increased risk of:
  - miscarriage, 14% cf 7%
  - low birth weight
  - premature birth
  - decreased ARGAR Scores
  - minor anomalies
  - admission to NICU
  - poor neonatal adaptation

- No increased malformations
- Some perinatal syndromes
- Chambers study... (2010)
  - increased risk of minor malformations
  - increased risk of preterm labour
  - increased admission to special care
- Extensive data which is mostly reassuring

Birth Outcomes in Pregnant Women Taking Fluoxetine By Christina D. Chambers, B.A., Kathleen A. Johnson, B.A., Lyn M. Dick, B.A., Robert J. Felix, B.A., et al.

Other SSRI's

- No increase in
  - congenital malformations
  - miscarriage / stillbirth

- Increased preterm labour.

- Decreased APGAR scores

- Problems in "neonatal adaptation" (previously reported as withdrawal syndromes) especially with paroxetine .

Benzodiazepines

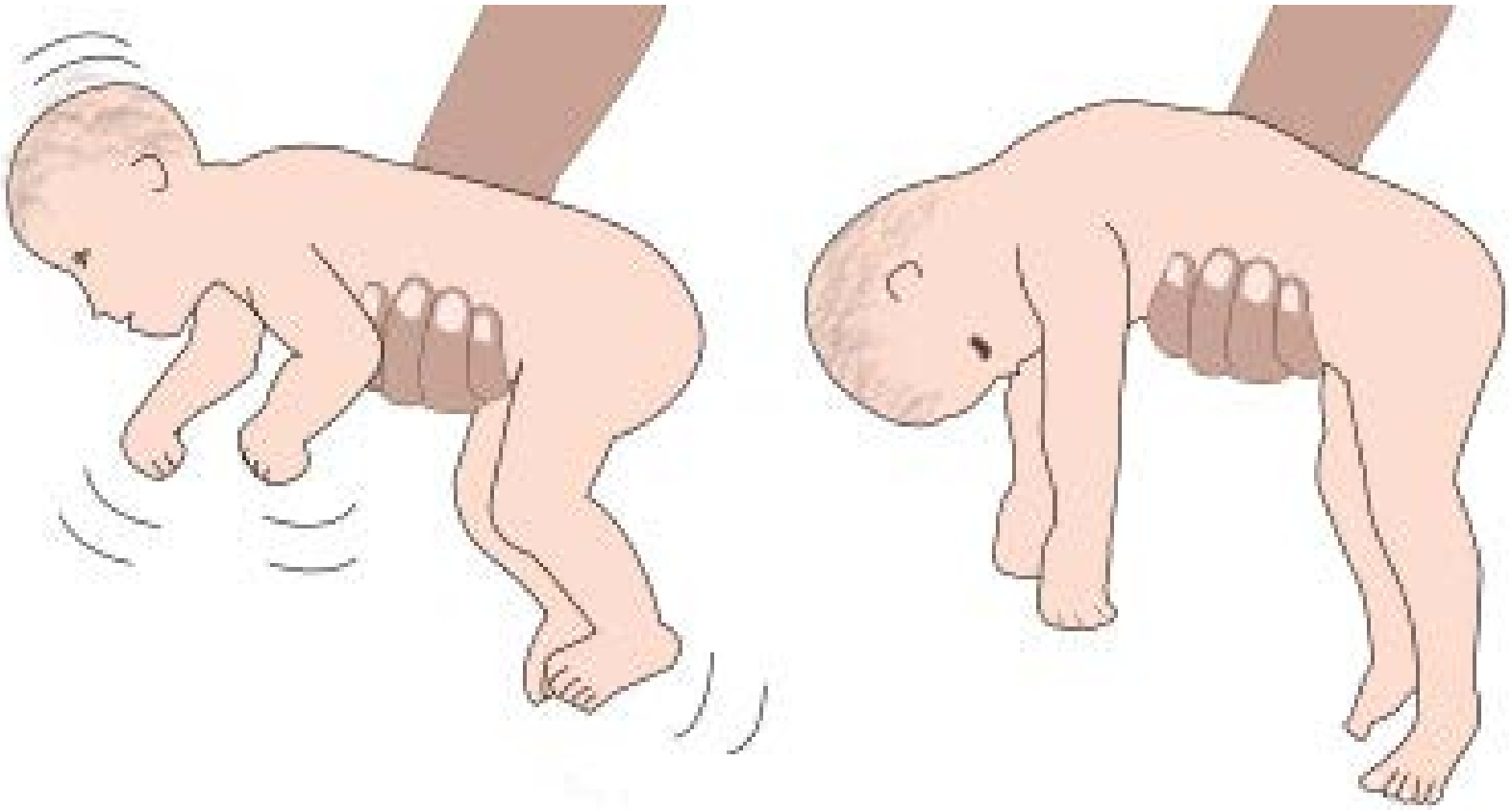
- High cortisol levels are problematic for the foetus which occurs in anxiety disorders.
- And benzodiazepines are contraindicated because of

➢ Neonatal sedation or withdrawal

➢ Floppy baby syndrome (baby is not responsive and listless)

➢ Oral Cleft Palate?

  – This is controversial 0.6% cf 0.06%
  – Some studies dispute this
  – Risk period is 6 - 9 weeks hence avoid during this period



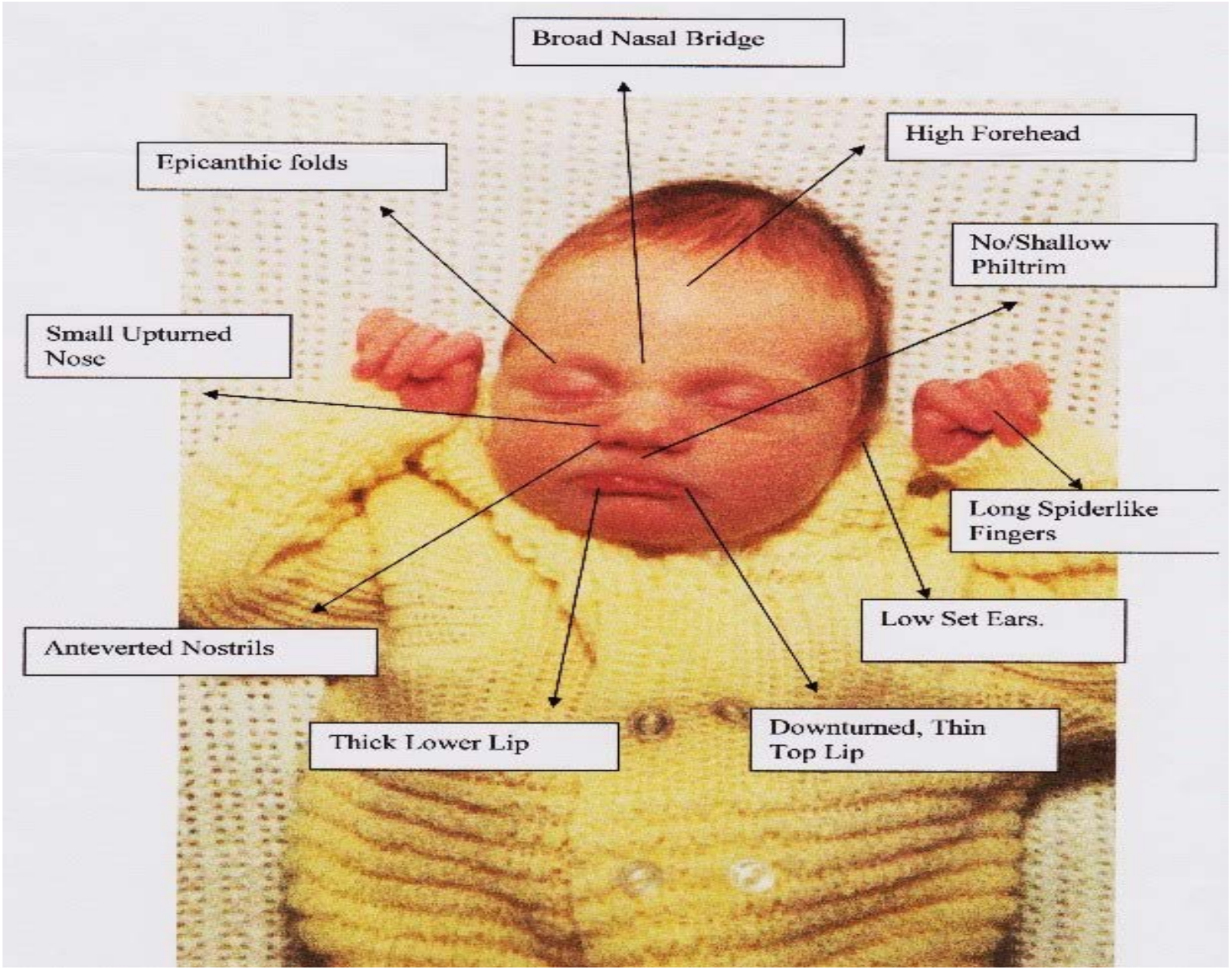
Normal Baby

Floppy Baby

Anticonvulsants/Mood stabilizers

Valproate

- The most dangerous psychotropic medication.
- 5 times higher rate of malformations or pregnancy complications.
- Neural tube defects increases from 0.3% to 1-5%
  [may be reduced by folate supplementation 4mg/day]
- Increases defects in heart/limbs/genitals/CNS and face.


Broad Nasal Bridge
High Forehead
Epicanthic folds
No/Shallow Philtrim
Small Upturned Nose
Long Spiderlike Fingers
Low Set Ears.
Anteverted Nostrils
Thick Lower Lip
Downturned, Thin Top Lip

Using Valproate.

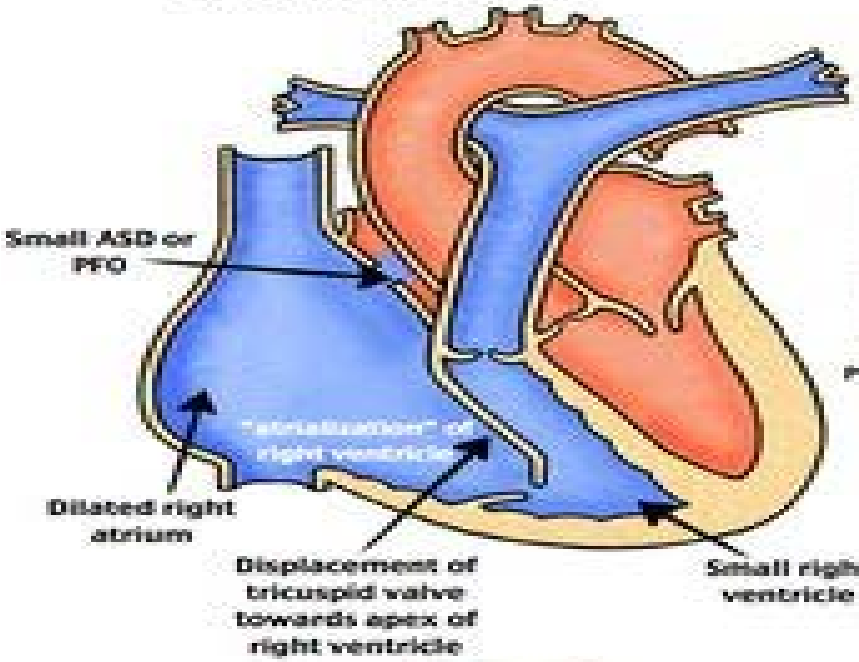
- Supplement with folate 4 mg per day from 4 weeks pre conception to 12 weeks gestation.
- Check foetal alpha-fetoprotein.
- Do high resolution ultrasound at 16 -18 weeks.
- Give vitamin K in final month of pregnancy.

Lithium

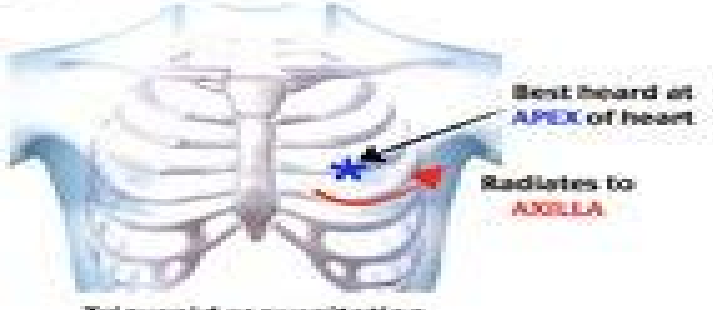
- Increases Ebstein's abnormality by 10 - 20 times (1 in 1000 cf 1 in 20,000)
- Foetal diabetes insipidus can occur.
- Floppy baby syndrome.
- Give in small divided doses if possible.

Ebstein's Anomaly

Congenital heart defect



Associated with Wolff-Parkinson-White syndrome



Tricuspid regurgitation

Carbamazepine

- The data is quite concerning.
- Associated with many different adverse outcomes in pregnancy.
- Increases the rate of neural tube defects but not as much as valproate. Overall malformation risk is doubled.
- Deficiency in Vitamin K dependent clotting factors associated with foetal intra-cerebral haemorrhage.

Lamotrigine

- A prospective trial did not show increased risk for major malformations but small sample size.
- Supplement with folate throughout pregnancy.

Antipsychotic drugs

Typical antipsychotics

- High potency drugs: eg haloperidol
- Neonatal extra pyramidal signs, are self limiting and resolve.
- No known teratogenicity based on surveillance data.
- Low potency drugs: eg chlorpromazine
- Neonatal anticholinergic symptoms.
- ?Some teratogenicity not supported by surveillance data.

Atypical antipsychotics
Olanzapine

- An atypical antipsychotic used increasingly in psychotic disorders.
- One prospective study showed no increased risk in pregnancy but small sample size.
- Breastfeeding: Limited information.
- Some case reports of adverse effects, but ?if related to the medication.

Summary.

- Goal is to *balance* the reduction of exposures from both *illness* and *medication*
- The severity of the illness tends to determine the options.
- Use a medication of prior response and,
- Use a medication of prior infant exposure.
- Use a medication with data.
- Try to use monotherapy.