

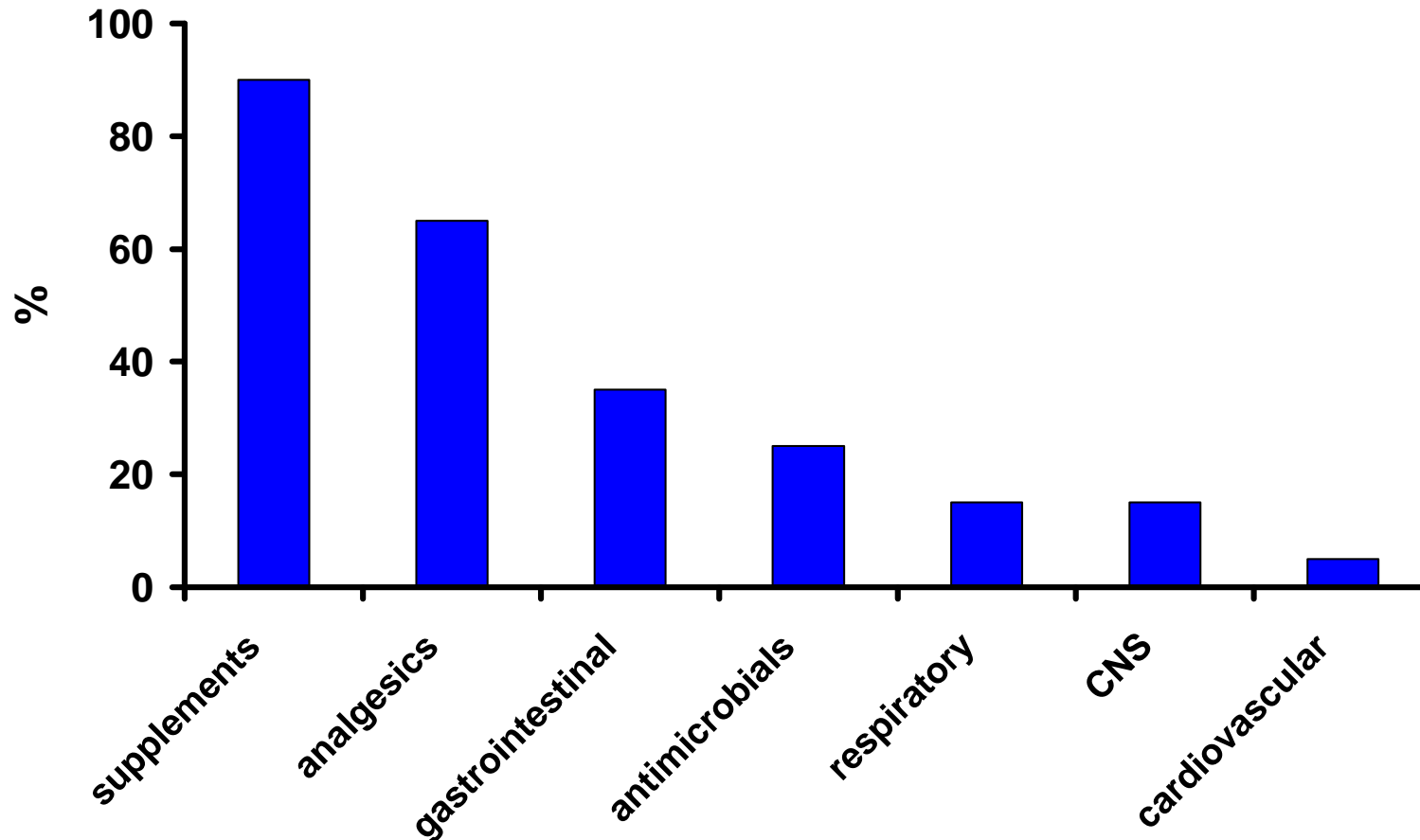


Medicines in Pregnancy

Dr Treasure McGuire

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Fact 1: Pregnant women use drugs



95% of women take 4 or more drugs at some stage of pregnancy
(based on data collected for 82,525 mother child pairs)



Developmental Stages

Week

0-2 **Conception**
Blastogenesis

Nutrients / Drugs are transferred into luminal

2 **Implantation**

secretions of fallopian tube & uterine cavity through which ovum then blastocyst must pass.
Drugs can kill but cannot cause congenital malformations

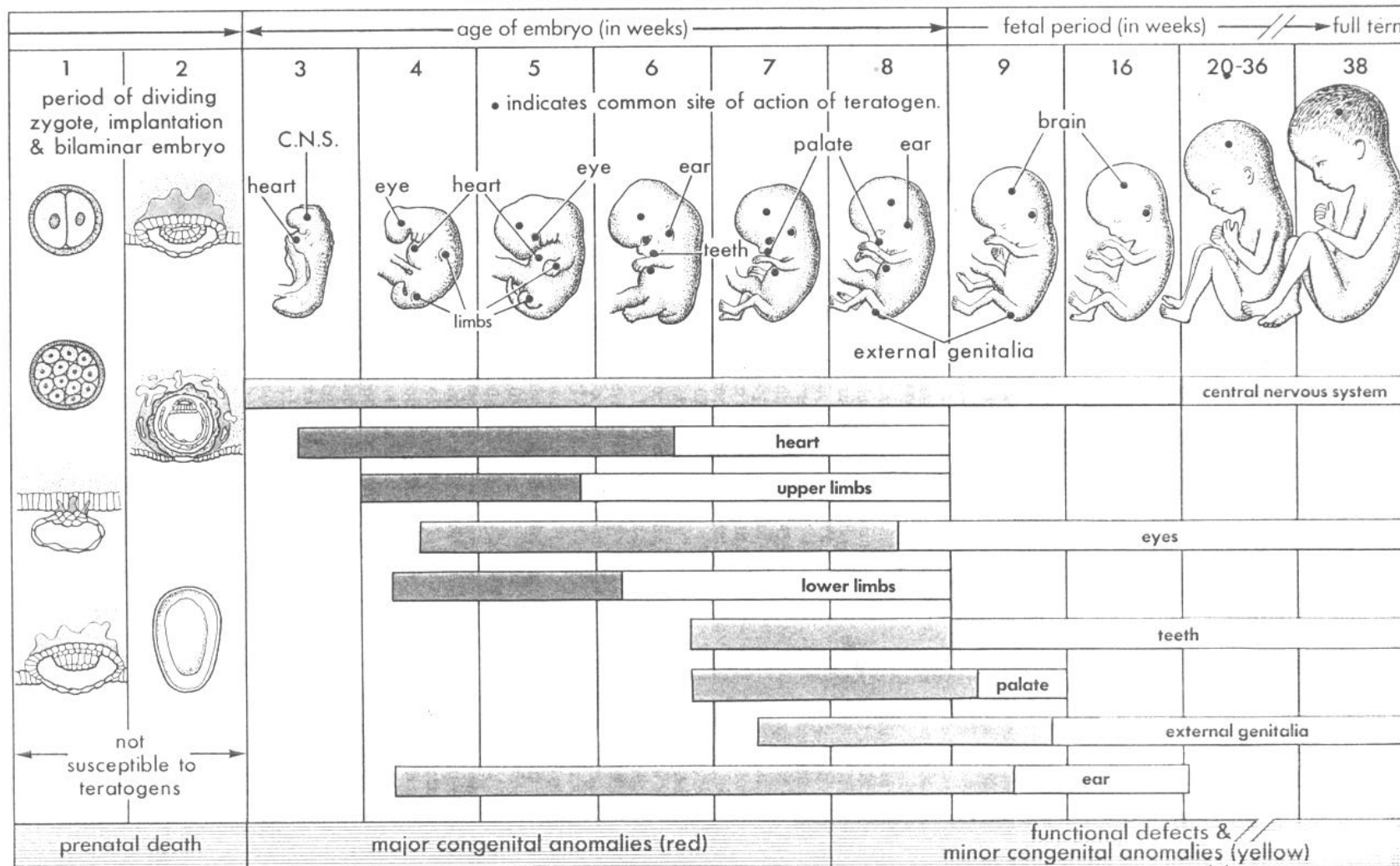
2-8 **Embryogenesis**

- have a direct connection between maternal & fetal circulation
- period of organ formation
- eg. Heart - days 18 - 40
- Brain - days 18 - 60
- Eyes - days 25 - 40
- Limbs - days 25 - 38
- Genitalia - days 40 - 60

8 - >22 **Fetogenesis** / fetal Toxicity (especially in the last 10 weeks prior to delivery)

- also complete closure of palate
- differentiation of external genitalia -> *pseudohermaphroditism*
- histogenesis of CNS ---> postnatally -> *behavioural / mental changes*

CRITICAL PERIODS IN HUMAN DEVELOPMENT*



* Red indicates highly sensitive periods when teratogens may induce major anomalies.

Tuchmann-Duplessis H. Drug effects on the fetus. New York: ADIS Press; 1977.



To be a Proven Teratogen a Drug must:

1. Produce deformities in > 2-3% of mothers exposed
 - Approx. 2-3% of all babies not exposed to drug therapy have congenital anomalies
 - Incidence of minor abnormalities such as birth marks, skin tags is around 7%
2. produce a consistent pattern of deformities

Difficulties

- *need large numbers of patients*
- *need to exclude other possibilities*

To Produce a Malformation, the drug must not only be given

- (1) In Sufficient Dosage (dose related effect) BUT
- (2) Embryo must be Sensitive (species specific)
- (3) Drug must be given at the Precise Moment the Target Organ is Forming ie the susceptible stage of development
- (4) Maternal pathophysiology also plays a role



ADEC Pregnancy Categories

A: taken by a large number of pregnant women without ANY PROVEN increase in the frequency of malformations or other direct harmful effects on fetus.

B: Taken by only limited numbers of pregnancy women, without an increase in frequency of malformation etc

AND WRT ANIMAL STUDIES:

B1 Show no evidence of fetal damage

B2 Inadequate but avail. Data show no evidence of fetal damage

B3 Have shown evidence of increased occurrence of fetal damage, but human significance uncertain.

C: Suspected of causing harmful effects BUT NOT MALFORMATIONS in HUMAN FETUS; may be REVERSIBLE.

D: Suspected or expected to cause an increased incidence of HUMAN FETAL MALFORMATIONS or IRREVERSIBLE DAMAGE.

Cat.D drugs not absolutely contraindicated (e.g. anticonvulsants); In some cases assigned on basis of `suspicion'. Due to legal considerations, sponsors have, in some cases, applied a more restrictive category than can be justified on available data.

X: High risk of permanent damage in the fetus

Pregnancy assoc condition

e.g. Morning sickness

- occurs in 70% of pregnancies (1:1 mild: severe)
- us. appears wks 4-8 & disappears by wks 14-16;
- aetiology unknown
 - ?linked with inc. HCG levels
 - ?neural &/or endocrine changes
 - ?Progesterone-induced relaxation of stomach's smooth muscle & gut stasis
- In hyperemesis gravidarum:
 - metabolic acidosis; disturbances; wt loss

Tx/Px

- Prevent dehydration!
 - fluid/electrolyte replacement (po/ IV)
 - Carbonated drinks can help
- Pyridoxine (Vitamin B6)
 - up to 3 times a day can help some women.
- Antiemetics
 - Metoclopramide, prochlorperazine, promethazine, chlorpromazine, (doxycycline), considered safe in 1st trimester
 - recommendation for further exploration of ginger root in both nausea and vomiting (Jewell and Young, 2003)



Constipation

- Safe to take
 - Bulk forming laxatives
 - eg Metamucil
 - Surfactants
 - E.g. Coloxyl
 - Osmotic laxatives
 - Lactulose, sorbitol, **Mg SO4**
- **AVOID**
 - Stimulant laxatives – uterine & gut both contain smooth muscle, if stimulate may stimulate the other!



PIH/ pre-eclampsia

- occurs in 3-8% of pregnancies; after approx 20 wks gestation
- sl. inc. incidence in primagravida
- incidence 2-3 times higher in diabetics & pts with pre-existing renal disease.

Presentation:

- generalised vasoconstriction;
- assoc with :
 - coagulation changes (TXA2 released during platelet aggregation & occlusive-thrombotic lesions may develop in renal &/or utero-placental circulation;
 - inc BP (systolic inc of >30 mmHg)
(diastolic inc.of >15mmHg)
 - proteinuria
 - oedema



PIH/ Pre-eclampsia

variant = HELLP syndrome

- ie. haemolysis, elevated liver enzymes' low platelet count
- although minimal inc in BP & renal dysfunction; the liver disease, coagulation & platelet changes are life threatening.
- **Tx of hypertension**
 - **Methyldopa**
 - most extensively used (normal physical & mental fetal development with 10 year follow-up)
 - 0.5-4g/day

- **Selective beta blockers**

- atenolol 50-200mg/day
- metoprolol 50-200mg/day
- oxprenolol 40-480mg/day
- widely used as gradual onset & lack of postural hypotension
- monitor of IUGR, fetal bradycardia, respiratory distress

- **Non-selective beta blockers**

- eg propranolol
- more likely to induce uterine contractions, bronchospasm, inc. sensitivity to insulin than selective agents.

- **Labetalol**

- combined alpha & beta blocker
- theoretically preferred as dec. peripheral resistance without changing CO or producing tachycardia

- **Prazosin** (limited use)



Tx of Pre-eclampsia

1. Lower BP

■ *hydralazine*

- (5-10mg iv bolus then infusion);

■ *diazoxide*

- (30mg iv bolus q 5 mins) to prevent excessive hypotension;

■ *nifedipine*

- (po/sl) as a uterine muscle relaxant

2. Maintain urine output

- >0.5ml/kg/hr
- add IV fluid if reqd

3. Px/Tx convulsions

□ *magnesium sulphate* (iv)

- peripherally has a curare like effect on NMJ, dec. Ach release, dec. contraction of vascular smooth muscle;
- also central action
- also tocolytic (can delay labour)

□ *phenobarbitone*



Drugs to avoid in Tx of PIH

■ ***Diuretics***

- cause plasma volume contraction

■ ***ACE Inhibitors***

- can cause fetal hypotension; IUGR; oligohydramnios; oliguria; renal failure; stillbirths.
- effects reported with use in 2nd & 3rd trimesters not in 1st trimester.



Thromboembolic disorders

- inc. risk of thromboembolic disorders in pregnancy:
 - dec. venous return from lower limbs;
 - inc. concs. of clotting factors
 - trauma assoc with delivery.

- *Most common thrombotic disorder is superficial thrombophlebitis*
vs
- *life threatening thromboembolism.*



Thromboembolic disorders – Px/Tx

□ *Heparin*

- recc for high risk pts eg Hx of clotting disorders;
- dose 5000 - 10,000 iu bd-tds
- safe as can't cross placenta
- monitor for HITTs

□ *LMW heparin*

- less experience than with heparin
- considered relatively safe in pregnancy

□ *Warfarin*

- not recommended
- crosses the placenta & assoc with birth defects from 1st trimester use;
- 2nd & 3rd trimester assoc with eye defects, inc. risk of fetal haemorrhage

Common Psychiatric drug families

DRUG	BIRTH DEFECTS	TOXICITY / WITHDRAWAL Sx
BENZODIAZEPINES e.g. diazepam (Valium) (C)	No (? McBride)	Yes (hypotonia)
TCA's (C)	No	Yes
Most SSRIs e.g. sertraline (Zoloft) (C)	(No)	Yes
PAROXETINE (an SSRI) (D)	(+/-) Heart defects	Yes
PHENOTHIAZINES e.g. trifluoperazine (Stelazine) (C)	No	Yes
ATYPICAL ANTIPSYCHOTICS e.g. olanzapine (Zyprexa) (B3)	No	Yes
LITHIUM (D)	Yes Heart defects	+/- changes in TFTs
CARBAMAZEPINE (Tegretol)	(+/-) is used	Yes
VENLAFAXINE (Efexor) (B2)	No	Yes
OTHER Mirtazapine (B3); Moclobemide (B3) Mianserin (B2)	No	Yes




Sertraline in Pregnancy

- Animal data
 - decreased growth at 20 times the human mg/kg dose
- Clinical data:
 - Prospective study of 147 women followed after contacting a CMIS wrt their use of sertraline. Incidence of malformations comparable to unexposed control subjects.
 - Offspring of 112 women who used sertraline (all trimesters) found not to have an increase in birth defects c.f. a control population.
 - Transition difficulties at birth and admission to a special care nursery were associated with late pregnancy exposure to the medication. (Cat C!)
 - Case report
 - symptoms of sertraline withdrawal in infant whose mother ingested drug through gestation & 1st 3 wks postpartum.
 - 1 day after drug cessation:
 - Sx of agitation, poor feeding, constant crying & insomnia. (intense for 48 h and subsequently subsided).
 - authors suggested that withdrawal Sx had been offset by residual levels of sertraline or active metabolites in breast milk.



Paroxetine – FDA alert (Dec 05)

- Category changed from C to D
 - ***Based on preliminary epidemiological data***
 - Study using Swedish national registry data Women receiving paroxetine early in pregnancy had a 2-fold increased risk for cardiac defect of entire national registry population (2% vs 1%)
 - US Insurance claims database – cardiac defects (1.5% paroxetine vs 1% other antidepressants).
 - Most were atrial or ventricular septal defects
 - Where wall between R & L sides of heart not completely developed
 - Also a common non-drug related malformation
 - Severity ranged from “asymptomatic & may resolve on own” to “symptomatic requiring surgery”



Fetal Toxicity (*1^o 3rd Trimester*)

Most Psychiatric drugs are associated with fetal toxicity

e.g Tricyclic Antidepressants

- possible long or difficult labour as fetus may be sedated (due to drug accumulation)
- Neonatal withdrawal symptoms likely
 - *irritability, tachycardia, muscle spasms, convulsions, urinary retention in neonate.*