MEDSCI 722

Drug disposition in pregnancy

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Te Whare Wānanga o Tāmaki Makaurau

1. Drug administration during pregnancy

Drug administration in pregnancy

- One of the most neglected areas in drug development and clinical pharmacology
- Only a handful of drugs have been approved by FDA
- Drugs are given to treat the mother but the fetus is always a recipient
- The pharmacologic and toxic effects of drugs are governed by a complex but integrated set of variables, which are constantly changing throughout pregnancy

Drug Categories in Pregnancy

- **Category A:**
  - Adequate controlled studies in human demonstrate no risk.
- **Category B:**
  - Animal studies indicate no risk, but there are no adequate studies in human.
  - Animal studies show adverse effects, but adequate studies in human have not demonstrated a risk.

Drug Categories in Pregnancy

- **Category C:**
  - A potential risk, when:
    - Animal studies have not been performed or,
    - Animal studies indicated adverse effects and,
    - There are no data from human studies.
  - These drugs may be used when potential benefits outweigh the potential risks.

Drug Categories in Pregnancy

- **Category D**:
  - There is evidence of human fetal risk, but the potential benefits to the mother may be acceptable.
- **Category X:**
  - Studies in animals or humans or adverse reaction reports or both have demonstrated fetal abnormalities.
  - The risk of use in a pregnant woman clearly outweighs any possible benefit.

Drug administration in pregnancy

- More than 50% of pregnant women receive some form of drug during pregnancy (mainly category B and C)
  - ~40% of drugs used has no evidence of safety in pregnant women
- Drug administration is more common earlier in pregnancy, when the developing fetus is most susceptible to xenobiotics
- Up to 1:20 pregnant women (5%) take a category D or X drug in their pregnancy

See: TERIS (Teratogen Information System):
http://depts.washington.edu/~terisweb/teris/

Drugs prescribed during pregnancy with possible teratogenic effects

- Anti-epileptics – valproate and phenytoin to be avoided (some evidence of increased risk) but congenital malformation rate <5% (monotherapy best)
- Steroids – androgens (virilization), estrogens (reproductive cancers/malformations)
- Antibiotics – streptomycin/kanamycin (hearing defects); tetracyclin (impaired teeth and bone formation)
- Non-steroidal anti-inflammatory drugs – (oligohydramnios, cardiovascular)
- Anti-depressants – SSRIs e.g. fluoxetine (now thought to be safe)
- Anti-fungals – fluconazole (multiple tissues/organs)
- Anti-retrovirals - protease inhibitors, RT inhibitors
- Anti-hypertensives – β blockers, ACE inhibitors, Ca channel blockers
- Anti-thrombotics – warfarin (CNS, skeletal, growth retardation, multiple)
- Anti-neoplastics/chemotherapeutics – Cyclophosphamide (multiple, growth retardation)
- Anti-psoriatics – etretinate (CNS, craniofacial etc)
- Anti-parasitics – chloroquine, abermectin
- Immune supressants – cyclosporine (growth retardation)

Non-prescription drugs taken during pregnancy

- Recent survey showed that >95% or pregnant women took over the counter drugs or supplements during pregnancy
- >75% took something other than vitamins etc
- >60% took OTC medicines
- 4% used herbal remedies
- >10% used four or more medications

!

Refuerzo et al, *Am J Perinatol* 22:321-4 2005

General Principles

- Drugs undergo a series of interactions in the body before producing the desired pharmacologic effect
- Number of variables can modify the intensity and duration of the effect
  - Rate and extent of absorption
  - Volume of distribution
  - Rate and nature of metabolism and excretion
  - Interaction with other compounds

Sex bias in trials and treatment

"Medicine as it is currently appliend to women is less evidence-based than that being applied to men" (Nature 465:665;2010).

- Sex differences in incidence, prevalence, symptoms, age at onset and severity have been widely documented.
- More women suffer from autoimmune disease than men. The reverse is true for autism.
- Women taking antidepressants and antipsychotics tend to have higher drug concentrations in their blood than men.
- Difference in drug sensitivity
  - Women require half as much influenza vaccine for the same level of protection as men.
  - Opiods such as pentazocine show a greater drug respons ein women, whereas ibuprofen produces a better response in men.
- women are more likely than men to experience adverse drug reactions
  - Eight out of 10 prescription drugs pulled from the U.S. market from 1997 to 2001 caused more side effects in women

Sex bias in trials and treatment

- Women have slower gastric emptying time and prolonged colonic transit time.
- There are also differences in the biotransformation of drugs
  - CYP3A4 is more active in women than in men. Theophylline and acetaminophen, which are metabolized by CYP3A4, are eliminated faster by women.
  - Drugs, such as diazepam, caffeine and some anticonvulsants, metabolized by CYP2C19 or CYP1A2 appear to be metabolized faster in men than in women.
- According to a recent study published in *Neuroscience and Biobehavioral Reviews*, out of nearly 2,000 animal studies published in 2009, there was a bias toward the use of male animals in eight of 10 disciplines (Beery and Zucker 2011).
- Clinical trials are men-centric as well. Women made up less than one-quarter of all patients enrolled in 46 examined clinical trials completed in 2004 (Geller et al., 2006).
- A recent study showed that women comprised only 10 percent to 47 percent of each subject pool in 19 heart-related trials, although more women than men die from heart disease each year (Kim et al., 2008).
- The most fundamental sex difference - pregnancy

http://statistically-funny.blogspot.co.uk/2013/04/women-and-children-overboard.html

2. Changes to maternal physiology during pregnancy

Physiologic – Pharmacokinetics Changes

- Physiologic Change:
  - 50% Increase in plasma volume and body water.
- Pharmacokinetic Change:
  - Water soluble drugs are distributed and "diluted" more than in the nonpregnant state.
  - Drug dosage requirements may increase.
  - This effect may be offset by other pharmacokinetic changes of pregnancy.

Physiologic – Pharmacokinetics Changes

- Physiologic Change:
  - Increased weight (~14 Kg) and body fat
- Pharmacokinetic Change:
  - Fat-soluble drugs are distributed more widely.
  - Drugs distributed to fatty tissues tend to linger in the body because they are slowly released from storage sites.

Physiologic – Pharmacokinetics Changes

- Physiologic Change:
  - Decreased serum albumin.
  - The rate of albumin production is increased. However, serum levels fall because of plasma volume expansion.
  - Many plasma protein-binding sites are occupied by hormones that increase during pregnancy.
- Pharmacokinetic Change:
  - More free drug is available for therapeutic or adverse effects on the mother and for placental transfer to the fetus.
  - A given dose of a drug is likely to produce greater effects than it would in the nonpregnant state.

Physiologic – Pharmacokinetics Changes

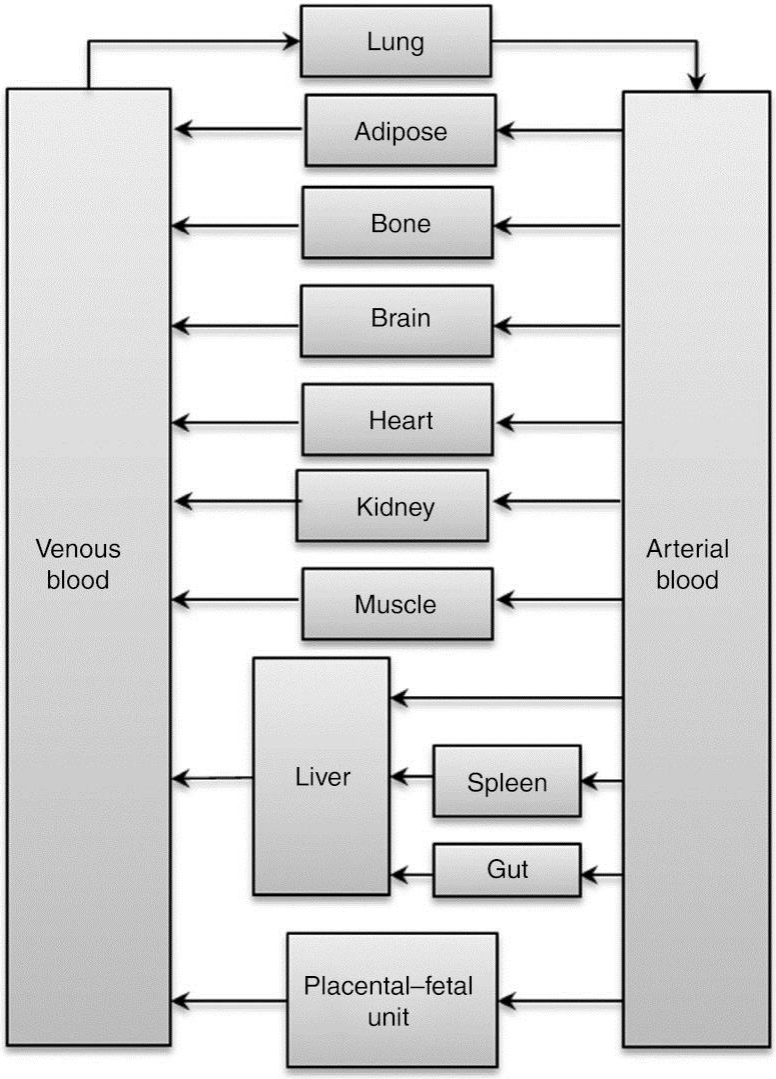
- Physiologic Change:
  - Increased renal blood flow and glomerular filtration rate secondary to increased cardiac output.
- Pharmacokinetic Change:
  - Increased excretion of drugs by the kidneys, especially those excreted primarily unchanged in the urine (digoxin, lithium).
  - In late pregnancy, the increased size of the uterus decreases renal blood flow in supine position.
  - This results in decreased excretion and prolonged effects of renally excreted drugs.

Pregnancy-induced enzyme-specific changes

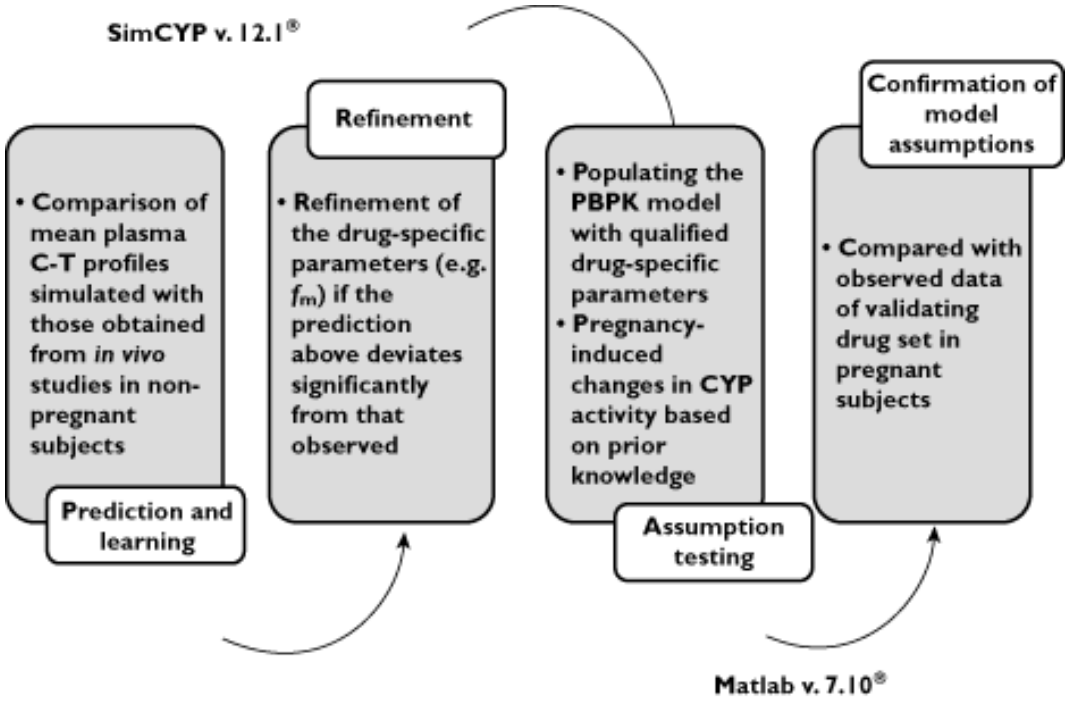
Enzyme	Pregnancy-induced change	Potential substrates in obstetrics	Possible clinical consequences
CYP3A4	Increased	Nifedipine, methadone, indinavir	Significantly lower trough levels of methadone during pregnancy associated with symptoms of withdrawal. Increase daily dose by 5–10 mg or administer in more frequent doses to avoid withdrawal
CYP2D6	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, citalopram	Increased metabolism of fluoxetine desmethylcitalopram, lower plasma levels of the drug are associated with recurring symptoms of depression
CYP1A2	Decreased	Theophylline, clozapine, olanzapine, ondansetron, cyclobenzaprine	Increase in theophylline half-life during pregnancy requiring dose reductions to avoid toxicity
UGT1A4	Increased	Lamotrigine	Significant decrease in lamotrigine concentration resulting in loss of seizure control, recommended to measure plasma lamotrigine concentrations during each trimester and adjusting dose as needed
UGT1A1	Increased	Acetaminophen	Increased acetaminophen glucuronidation resulting in decreased half-life, clinical consequences are unknown
NAT2	Decreased	Caffeine	Decreased metabolism of caffeine Clinical consequences are unknown

Feghali MN, et al. Journal of biomedicine and Biotechnology 2011. doi: 10.1155/2011/783528

Physiologically Based Pharmacokinetic (PBPK) model



Expansion of a PBPK model to predict disposition in pregnant women of drugs cleared via multiple CYP enzymes, including CYP2B6, CYP2C9 and CYP2C19



British Journal of Clinical Pharmacology
Volume 77, Issue 3, pages 554-570, 21 FEB 2014 DOI: 10.1111/bcp.12207
http://onlinelibrary.wiley.com/doi/10.1111/bcp.12207/full#bcp12207-fig-0001

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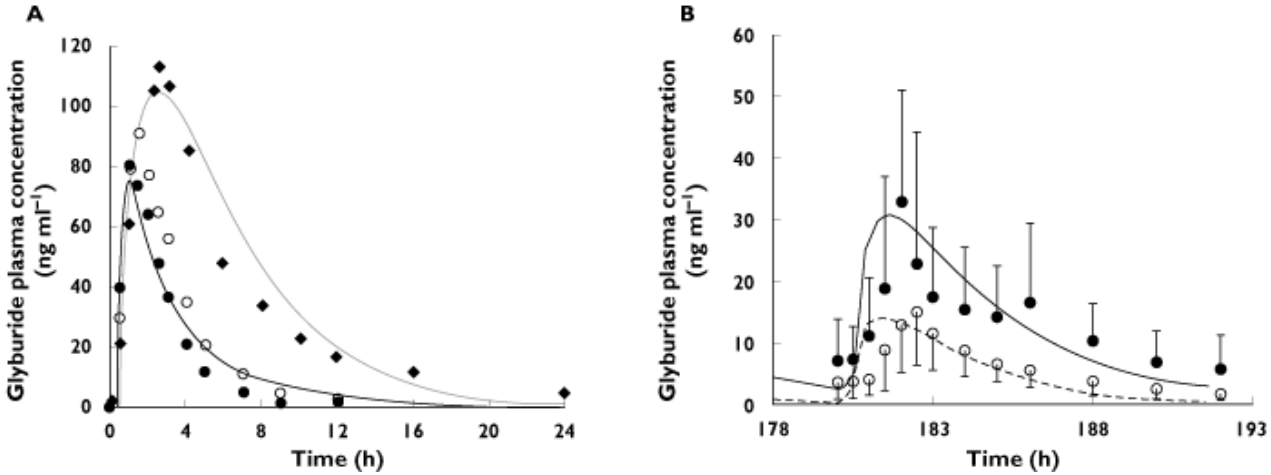

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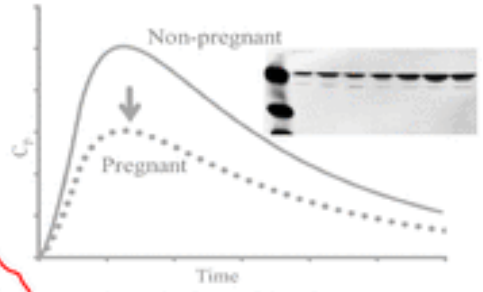
http://onlinelibrary.wiley.com/doi/10.1111/bcp.12207/full#bcp12207-fig-0005

In vivo human clinical studies

- Probe studies to address enzyme specific changes
- PBPK modeling of changes in probe and clinically relevant drug disposition
- Analysis of endogenous signaling molecules and their concentrations throughout gestation
- PBPK models of organ specific mechanisms



Correlation of *in vivo* changes and integration of mechanisms

Elaboration of mechanisms

Quantitative and qualitative prediction of pregnancy DMPK

Safety studies, rationalization of changes

In vitro evaluation

cell lines, hepatocytes and other tissue preparations

- Enzyme specific studies of regulation and existence of induction/down-regulation
- Potency and efficacy of hormones and other regulators
- Enzyme specific mechanisms

Confirmation of mechanisms, and integration with pregnancy

Mechanistic hypotheses

Animal studies

- Determine the effect of pregnancy on specific enzyme and transporter activity/expression
- In vivo mechanistic studies of gene regulation by hormones and other compounds
- Fetal exposure studies and toxicology

Changes in P450 probe and sensitive marker drug disposition and in disposition of UGT markers

Target P450	Marker Drug	Effect on Marker Clearance during Gestation		
		First Trimester	Second Trimester	Third Trimester
CYP1A2	Caffeine, theophylline	↓	↓	↓
CYP2B6	Efavirenz			↔↑[a]
CYP2D6	Metoprolol (dextromethorphan UR)	(↑)	(↑)	↑ (↑)
CYP2C9	Phenytoin	↔	↑	↑
CYP3A4	Midazolam			↑
UGT1A4	Lamotrigine	↔	↑	↑
UGT2B7	Zidovudine			↔

Drug Metab Dispos. Feb 2013; 41(2): 256–262.
Published online Feb 2013. doi: 10.1124/dmd.112.050245

Transporter	Marker Drug	Effect on Clearance during Gestation		
		First Trimester	Second Trimester	Third Trimester
P-gp	Digoxin			↑
OATP1B1	Glyburide[a]			↑
OCT2	Metformin	↔	↑	↔↑[b]
OAT1	Zidovudine, lamivudine			↔
OAT3	Acyclovir, zidovudine			↔

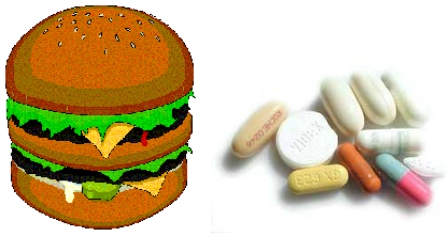
Drug Metab Dispos. Feb 2013; 41(2): 256–262.
Published online Feb 2013. doi: 10.1124/dmd.112.050245

3. Fetal exposure: placental transfer and metabolism of drugs

Maternal – Fetal Circulation

- On the maternal side, arterial blood pressure carries blood and drugs to the placenta.
- Drugs readily cross the placenta, mainly by passive diffusion.
- Placental transfer begins approximately the fifth week after conception.
- Drugs given on a regular schedule, equilibrate with fetal blood which contains 50% - 100% of the maternal blood.
- After entering the fetal circulation, large amounts of drugs are active because albumin levels are low and thus low levels of drug is bound.

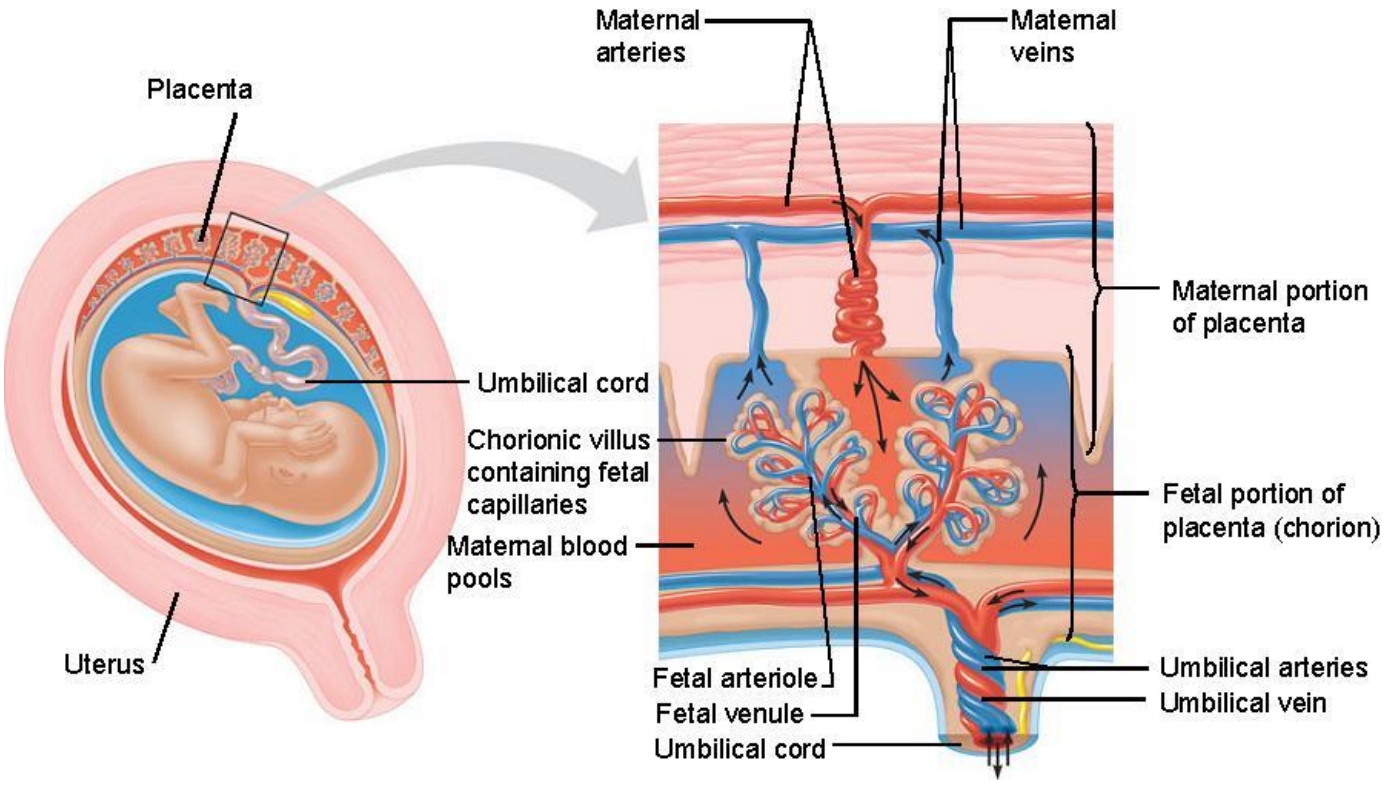
Drug disposition in the maternal-fetal unit



Maternal circulation ⟷ **Placenta** ⟷ **Fetal circulation**

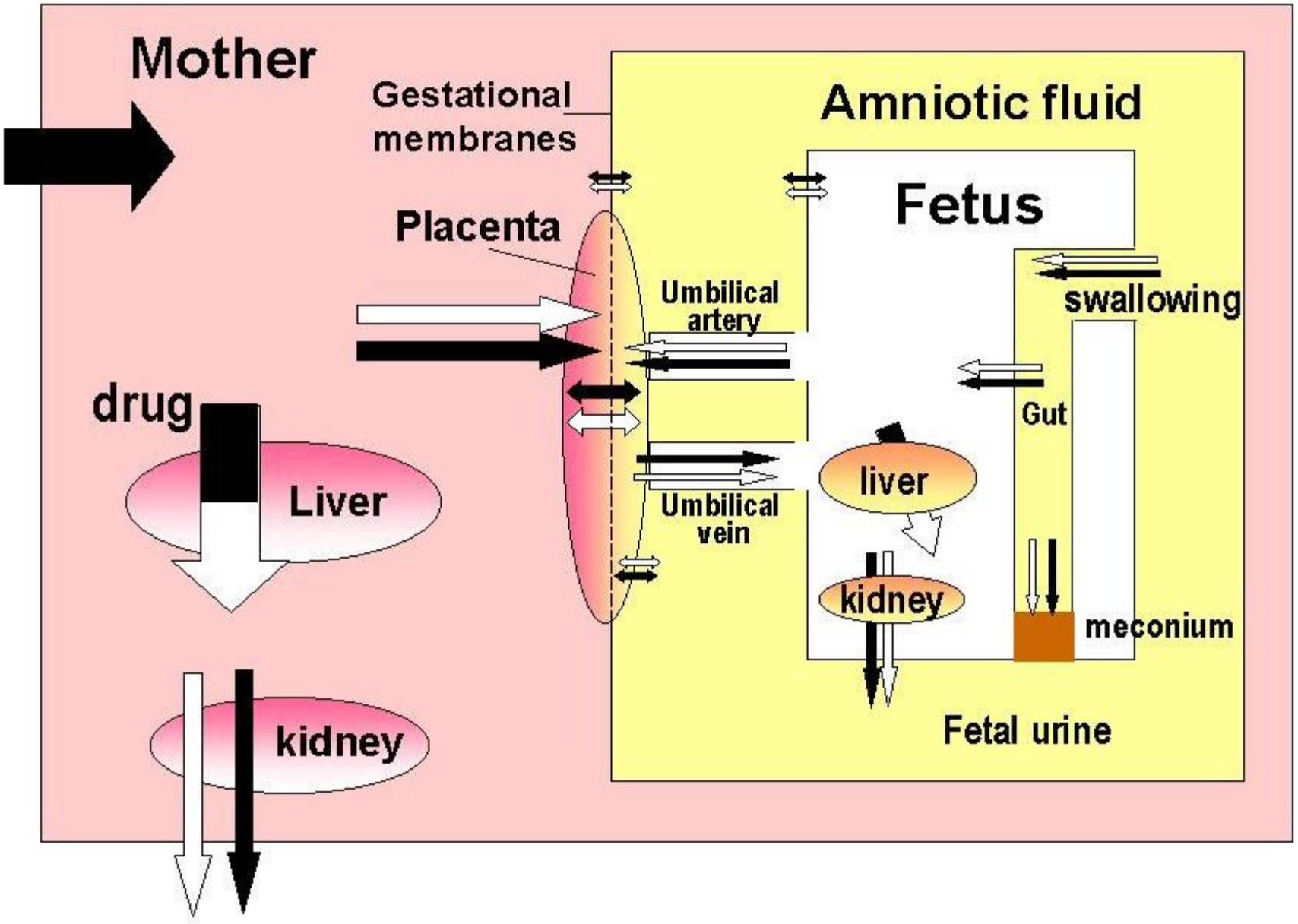
- ***Drugs that reach the fetus are (almost) always first administered to the mother!***

The Placenta



http://bio1152.nicerweb.com/Locked/media/ch46/placenta.html

Maternal-fetal drug transfer



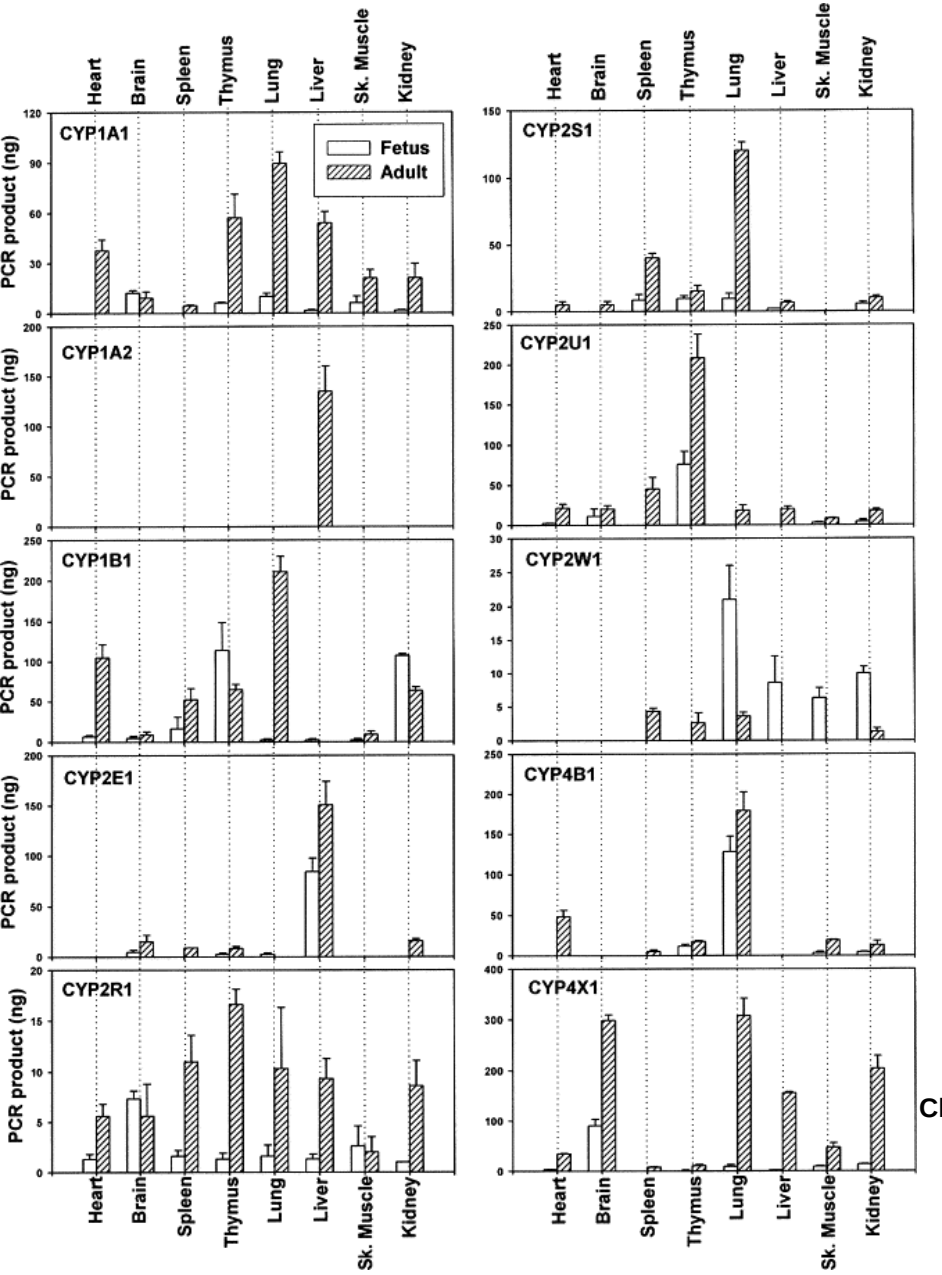
Fetal drug disposition

- Blood flow through the placenta (maternal side) increases during gestation (50 ml/min @ 10 weeks of pregnancy - 600 ml/min @ 38 weeks).
- Fetal plasma binding proteins differ from maternal concentrations: albumin 15% greater than maternal, but α1-acid glycoprotein ~37% lower
- Fetal plasma proteins also appear to bind some drugs with lower affinity than in adults (i.e. ampicillin, benzylpenicillin)
- Ion trapping: Fetal plasma pH < maternal: base drugs (i.e. lidocaine) more ionized on fetal side, less cross placenta back to maternal plasma = apparent accumulation in fetal plasma. Principle also applies to metabolites (more polar, less mobile)

Fetal drug metabolism and clearance

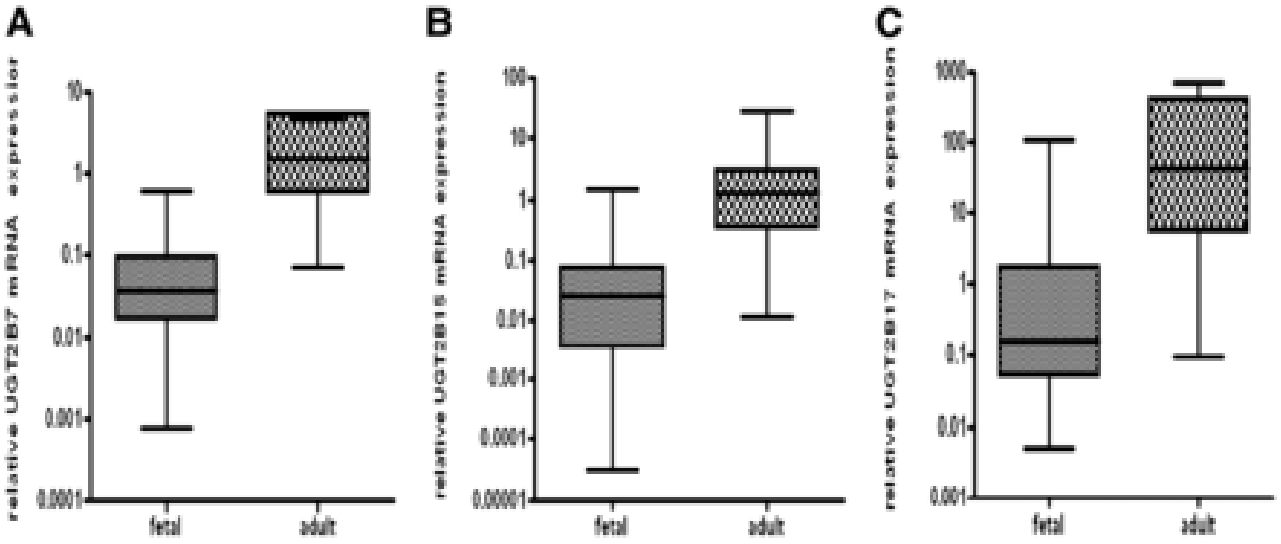
- Fetal liver expresses metabolising enzymes (i.e. CYPs), but metabolising capacity is less than that of mother (some enzymes are fetal-specific)
- Drugs transferred across placenta undergo 1st pass through the fetal liver before reaching systemic circulation (30-70% by pass)
- Fetal kidney is immature: GFR is reduced (~25% [size adjusted] of adult GFR for term fetus)
- Fetal urine (containing excreted drugs) enters amniotic fluid which may be swallowed by fetus and drugs reabsorbed (however, fetal renal output is only ~5% of blood flow)

Fetus Vs. Adult variations



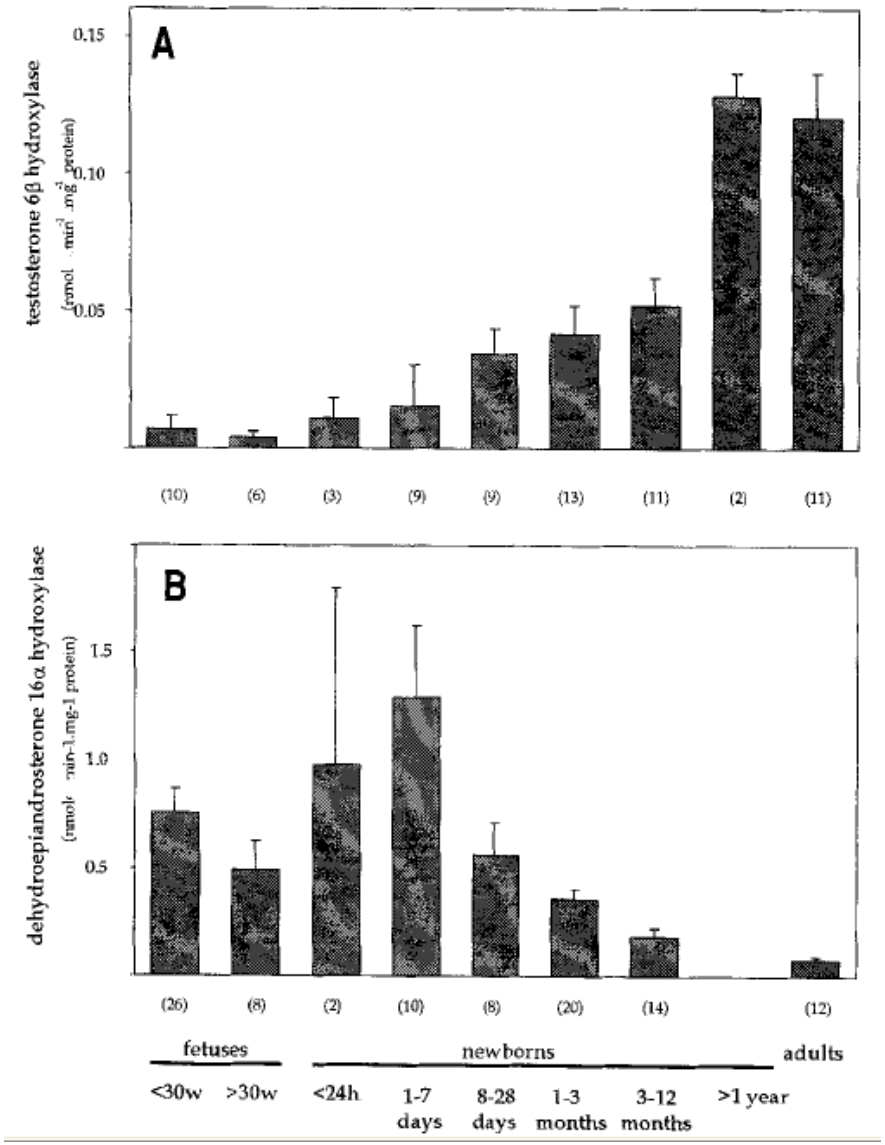
Choudhary et al., Archives of Biochemistry and Biophysics 2005:436 (1); 50-61.

Fetus Vs. Adult variations



Ekstrom L, et al., Drug Metab Dispos 2013; 291-295.

Age-related variations



CYP3A7 – Fetal
CYP3A4 - Adult

Lacroix et al., European Journal of Biochemistry 1997: 247; 625-634.

Placental drug disposition

Critical factors that affect drug transfer across the placenta:

- Physicochemical properties
  - lipid solubility, ionization, size, protein binding characteristics.
- Placental flow (flow-limited drugs)
  - Compounds that alter blood flow alter maternal drug disposition and placental transfer.
- Placental metabolism
  - Relatively minor compared to hepatic metabolism.
- Placental transporters
  - important for some (many) drugs

Role of Placenta in Limiting Fetal Drug Exposure

- Diffusion – MW ≤600 freely, 500-1000 some, >1000 poorly
- Placental Barrier composed of
  - Syncytiotrophoblast (apical maternal/basal fetal)
  - Fetal endothelium
- Drug metabolizing enzymes present in the placenta
  - May see loss of enzyme by term
  - Many data from mRNA and immunohistochemistry – activity may be lacking
- Drug transporters in placenta

Placental drug metabolising enzymes

- Phase I enzymes (dealkylation, hydroxylation, demethylation)

  Cytochrome P450s (many isoforms)

  Less active than the adult liver (only ~10%)

  Changes evident with gestational age

- Phase II enzymes (conjugation mainly)

  Glutathione-S –transferases (fetal protection against oxidative stress?)

  Epoxide hydrolase (protection against epoxides?)

  Sulphotransferases (sulfation)

  N-acetyltransferases (acetylation)

  Glucuronyl transferase (glucuronidation)

Placental drug transporters

- Xenobiotic transporters (drug efflux pumps) expressed in placenta
  ABC transporters (e.g Pgp/MDR1, MRP, BCRP) and members of the SLC family of solute transporters (gradient driven) plus others
- Changes in activity observed with gestational age (cellular composition) – regulated by steroids, growth factors, cytokines
- Major role in protecting fetus from drugs by pumping from placenta into maternal circulation
- Some appear to pump from placenta to fetal circulation!
- Polymorphisms (e.g. in Pgp or BCRP) may explain why some fetuses suffer from teratogenicity while majority do not

Transporter	Gene Symbol	Localization in Placental Syncytiotrophoblasts	Selected Substrate Drugs
P-gp	ABCB1	Apical	**anthracyclines (e.g. daunorubicin, doxorubicin) HIV protease inhibitors (e.g. indinavir, saquinavir) immunosuppressants (e.g. cyclosporine A) phenytoin, quinidine, ter- fenadine, paclitaxel, ketoconazole, loperamide, atorvastatin, methadone, digoxin, fexofenadine**
BCRP	ABCG2	Apical	**anthracyclines, mitoxantrone, nitrofurantoin, glyburide, methotrexate, prazosin, zi- dovudine, topotecan, SN-38, flavopiridol, pantoprazole cimetidine, imatinib, statins**
MRP1	ABCC1	Apical and/or basolateral	**etoposide, methotrexate, vinblastine, saquinavir, cisplatin, mitoxantrone, topotecan**
MRP2	ABCC2	Apical	**etoposide, methotrexate, paclitaxel, vincrstine, cisplatin, arsenite, rifampicin, pravas- tatin**
MRP3	ABCC3	Apical and/or basolateral	**methotrexate, etoposide, acetaminophen, adefovir**
MRP5	**ABCC5**	**Basolateral**	**methotrexate, nucleoside analogues**

Curr Pharm Biotechnol. 2011; 12(4): 674-685.

Effect of P-glycoprotein blocker on drug transport to the fetus

Effect of PSC833 on maternal plasma and fetal tissue levels of radioactivity 5 minutes and 15 minutes after intravenous administration of [^{14}C]saquinavir (1mg/kg)

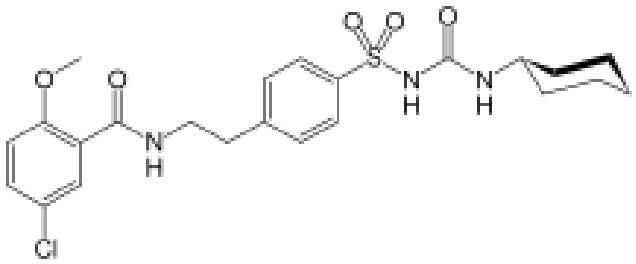
	[^{14}C]saquinavir + vehicle	[^{14}C]saquinavir + PSC833	PSC833/vehicle ratio
5 minutes			
Mdr1a$^{+/+}$/*1b*$^{+/+}$	3.5 ± 1.5	24.1 ± 4.8^{A}	6.9
Mdr1a$^{+/-}$/*1b*$^{+/-}$	4.3 ± 1.9	23.1 ± 5.5^{A}	5.4
Mdr1a$^{-/-}$/*1b*$^{-/-}$	16.5 ± 7.2	23.7 ± 5.6	1.4
Plasma	429 ± 32	1297 ± 247^{B}	3.0
15 minutes			
Mdr1a$^{+/+}$/*1b*$^{+/+}$	4.2 ± 0.6	26.3 ± 8.9^{B}	6.3
Mdr1a$^{+/-}$/*1b*$^{+/-}$	4.4 ± 1.0	20.9 ± 6.2^{A}	4.8
Mdr1a$^{-/-}$/*1b*$^{-/-}$	21.1 ± 3.4	26.0 ± 6.8^{C}	1.2
Plasma	146 ± 16	790 ± 195^{B}	5.4

Swit et al., JCI 1999: 104; 1441.

Glibenclamide

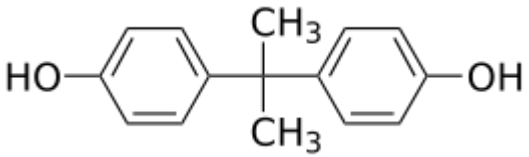
- Sulfonylurea drug for treatment of type II diabetes
- Very low maternal -> fetal transfer
  - High protein binding (>99.8%)
  - Short elimination half-life
    - Low Vd (0.2 l/kg)
    - Rapid clearance (1.3ml/kg/min)

  => Not much opportunity for free drug to cross the placenta!
- Evidence for active transport from fetal to maternal compartments – substrate for ABC transporters?



Glibenclamide

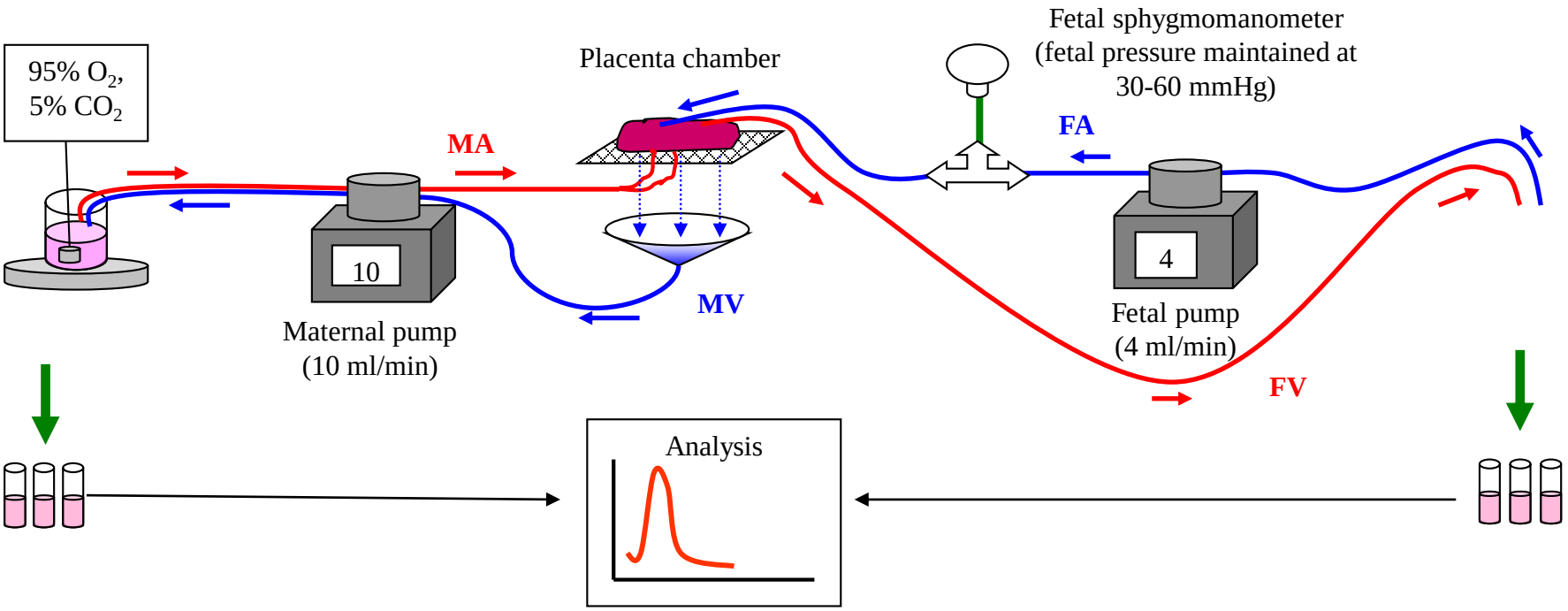
Bisphenol A (BPA)



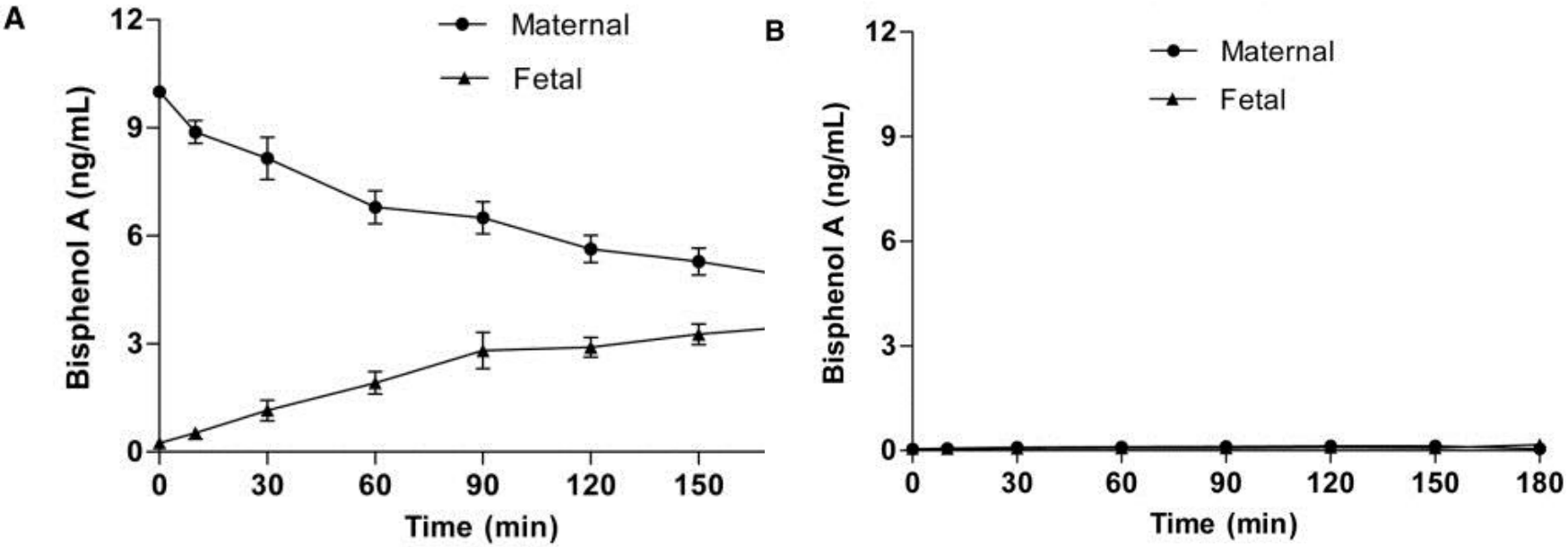
Bisphenol A

- Residual component of plastics manufacture
- Widely distributed in the environment
  - Adult daily intake ~1mg/kg/day
  - Infant fed formula from a polycarbonate bottle ~10mg/kg/day
- Estrogenic – animal studies show impacts on sexual development
  - But level of risk to humans hotly debated
- Current research at Liggins:
  - bisphenol A rapidly crosses the placenta
  - Not conjugated by placental enzymes

Placental perfusion model

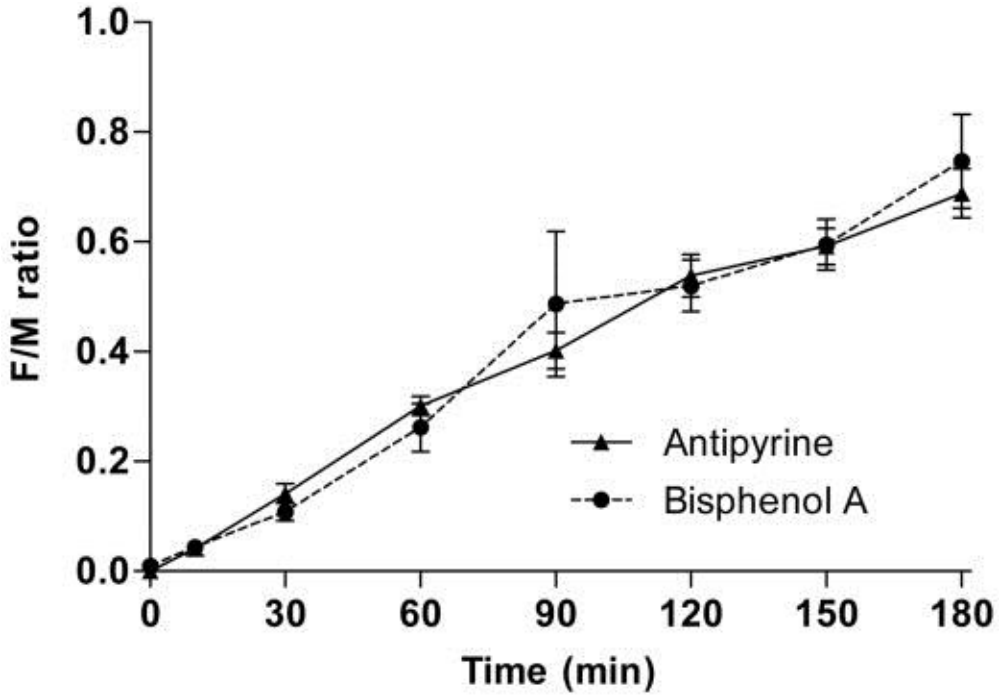


BPA transfer across human placenta



Balakrishnan et al., Placenta 2010: 202 (4); e1-e7.

BPA transfer across human placenta



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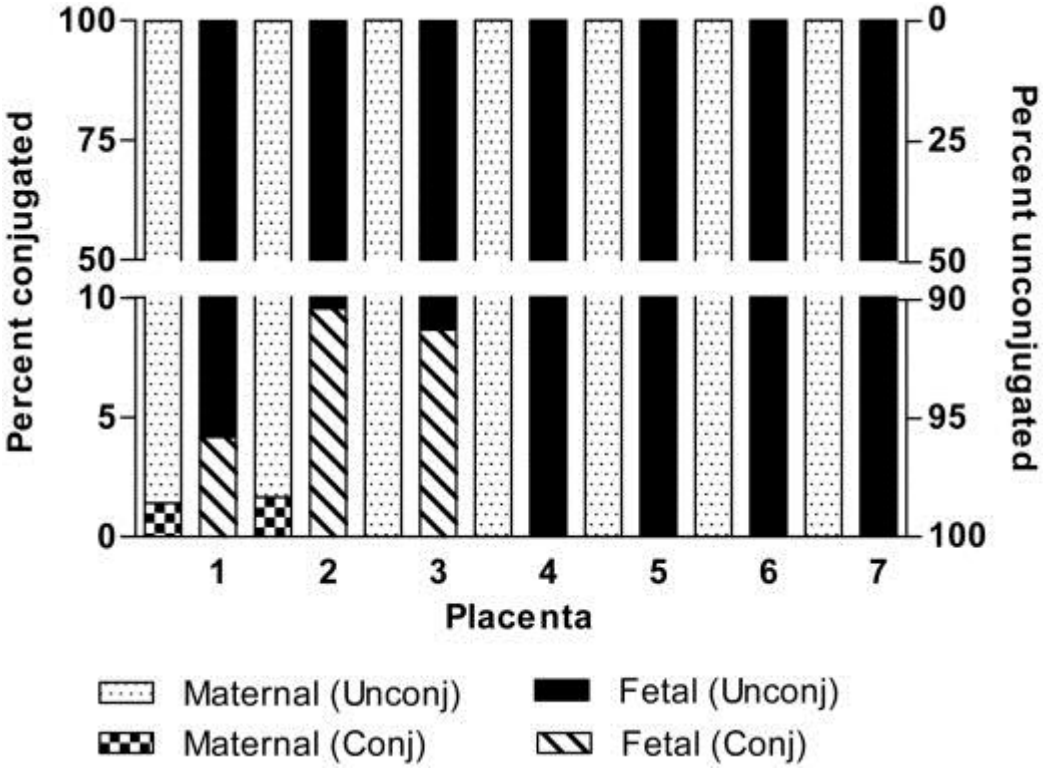
BPA transfer across human placenta



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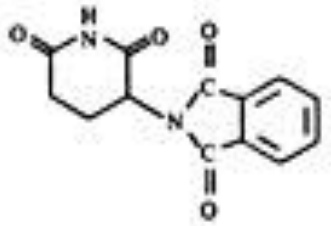
Mechanisms

- Effects on maternal tissues primarily, with only indirect (secondary) effects on fetus
- Direct effects on developing fetal tissues
- Indirect effects via interference with function of placenta, i.e. placental transfer or placental metabolism

Adverse effects of drugs on the fetus during pregnancy

- Teratogenicity (i.e. thalidomide) - readily detected at, or shortly after, birth
- Long term latency (i.e. diethylstilbestrol)
- Impaired intellectual or social development (i.e. exposure to phenobarbitone - alters programming of brain)
- Predisposition to metabolic diseases (i.e. Barker hypothesis - low birthweight associated with increased risk of diabetes, hypertension, heart disease in adulthood)

Example 1: Thalidomide



- Sold as a sedative, for coughs/colds, nervousness/neuralgia, migraine/headaches, asthma, nausea
- Sold in 11 European countries, 7 African countries, 17 Asiatic countries and 11 others (including Canada, Australia and New Zealand). Not sold in the USA (FDA approval not granted).
- Sold in many forms, either alone (25/100 mg tabs or in liquid form), or combined with other drugs (aspirin, quinine, bacitracin, dihydrostreptomycin):

  Algosediv, Asmaval, Calmorex, Enterosediv, Gastrimide, Grippex, Noctosediv, Peracon-Expectorans, Polygrippan, Prednisediv, Tensival, Valgis, Valgraine

Thalidomide trade names

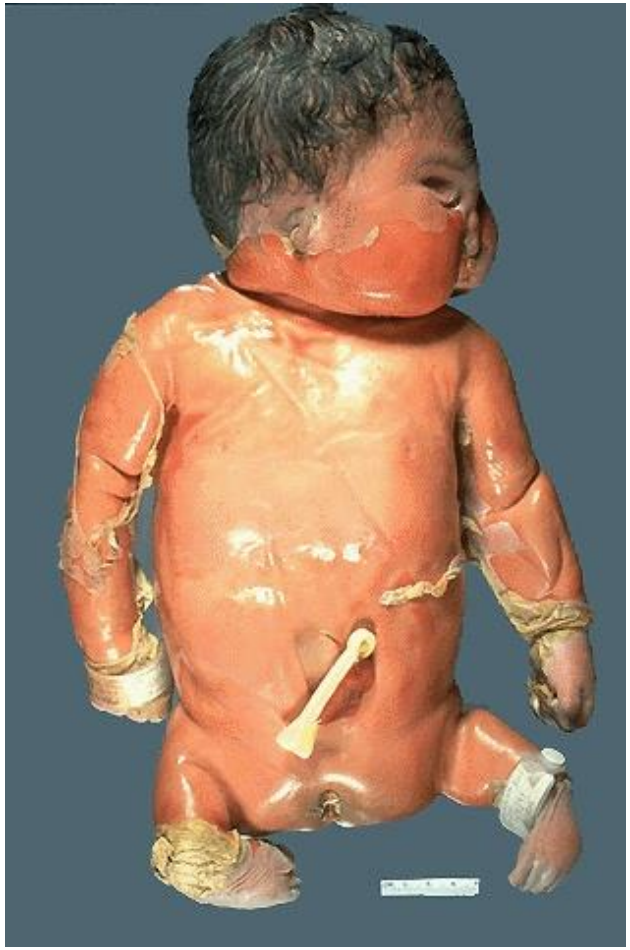
• UK/Australia/NZ	Distaval
• Canada	Talimol
• USA	Kevadon (not sold)
• Finland	Softenon
• Sweden	Neurosedyn
• Spain	Imidan
• Italy	Imidene/sedoval/quietimid
• West Germany	Contergan/softenon
• Portugal	Sedilab

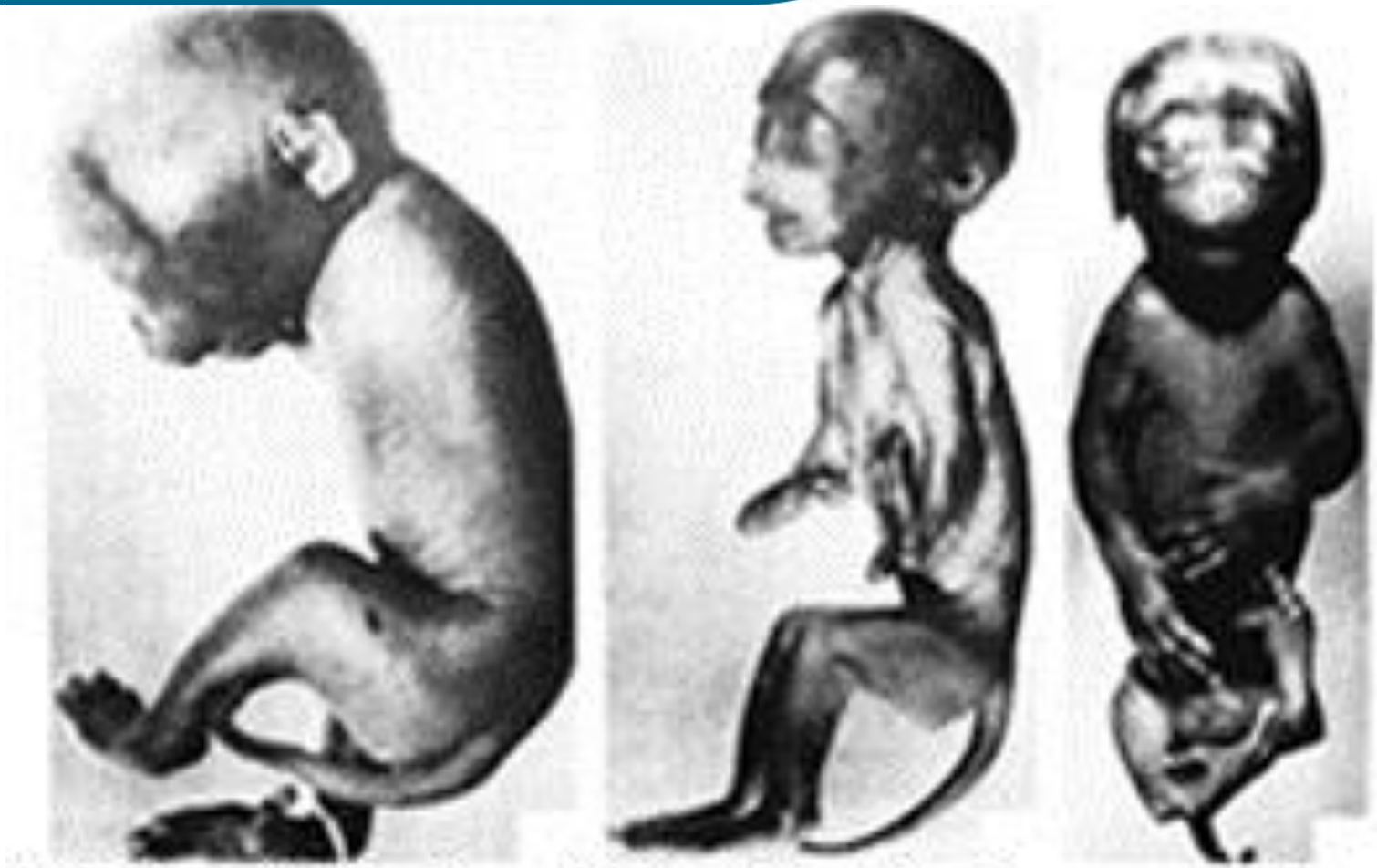
Some thalidomide facts

- 😐 Evidence of safety was from paid research by junior doctors in small numbers of patients
- 😐 Early evidence of parasthesia was ignored by Grunenthal and not reported in the literature
- 😐 Effects on mothers or babies never tested
- 😐 Effects on neural system never tested (polyneuritis common)
- 😐 Chronic toxicity studies never carried out
- 😐 Effects on liver not tested
- 😐 Drug interaction/metabolic studies never performed
- 😐 Stability and nature of decomposition products not characterised
- 😐 Its rate of absorption was unknown

Thalidomide-induced phocomelia

- Normal incidence of phocomelia (Greek: seal - limb) ~1 in 4 million.
- March 1962: Thalidomide-type malformations were reproduced in rabbits given thalidomide.
- 1965: Chemie Grunanthal stated on TV that teratogenic effects of thalidomide have not been able to be reproduced in monkeys (weeks earlier they had been shown the deformed embryos of monkeys given thalidomide between days 34-40 of pregnancy).





Thalidomide induced limb defects in rhesus monkey; micrognathia is also present (Schardein 1993).

Time-course of teratogenic effects of thalidomide

Time of ingestion (days after LMP)	Defect
34-38 days:	Ears/cranial nerves/thumb duplication
(39)42-48 days:	Severe limb abnormalities
40-45 days:	Gall bladder /duodenum/heart
50 days:	Thumb (minor)/rectum

Total global teratogenic effects of thalidomide

Country	Number of affected fetuses
Germany	5400-6700
Great Britain	400
Sweden	1000+
Others	1-2000
Total	***8-10,000 (survived)***
(corrected for deaths)	13-16,000 affected fetuses in total

Example 2: Diethylstilbestrol

- DES: Steroid analogue prescribed 1940-1970 to prevent miscarriage
- By mid 1970s cases of vaginal adenocarcinoma in women aged 16-20 were observed and finally linked to fetal DES exposure
- Approx 1:1000 pregnancies were exposed, 75% of which resulted in female offspring with vaginal/uterine carcinomas or uterine abnormalities
- Male children had abnormal genitalia or sperm defects

Example 3: Retinoic acid

- Isotretinoin (sold as Roaccutane in NZ) – category X drug
- Teratogenic even at very low doses (accumulates in tissues and effects can last months)
- Used to treat acne in young adults
- Fetal exposure results in craniofacial alterations, cleft palate, neural tube defects, impaired IQ and many other malformations
- Around 200,000 exposures during pregnancy – over 1000 fetal malformations, 1000 spontaneous abortions and 10,000 elective abortions due to Roaccutane exposure

Drug administration in pregnancy – useful references

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