
Welcome

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# Drugs in pregnancy, Labour, Postpartum: effects on the newborn

**Pregnancy** - whether planned

or unplanned ,

a pleasant or

an unpleasant surprise

always brings

# Prevalence of substance use in pregnancy – 2002/2003 (USA)

| **Substance** | Pregnant – % use | Non-pregnant % use |
|---|---|---|
| Alcohol - any | 9.8 | 53 |
| Alcohol - binge | 4.1 | 23 |
| Alcohol - heavy | .7 | 5.3 |
| Illicit drugs | 4.3 | 10.4 |
| Cigarettes | 18.0 | 30.7 |
| | | |

# Drugs in Pregnancy

- ~~Use only drugs which are extensively used in past~~
- Do not use new or untried drug
- Use smallest effective dose
- No drug is safe beyond all doubts in early pregnancy

# Drugs in Pregnancy

**FIRST TRIMESTER :**

congenital malformations (teratogenesis)

**SECOND & THIRD TRIMESTER :**

affect growth & fetal development

or

toxic effects on fetal tissues

**NEAR TERM :**

adverse effects on Labour

# Folic Acid Supplementation in Pregnancy

- Prevents Neural tube defects
- Decrease in homocystinemia (and heart disease)

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* Neural tube defects develop in the first 28 days after conception.
* "Once you know you're pregnant it's too late to do anything about [them],"
* Half of all pregnancies are unplanned

* The incidence of neural tube defects might be ↓ 45%

# Severe Pre eclampsia / HTN

- IV Labetolol (ß blocker):

- Side effects: headache, nausea, vomiting, postural hypotension & liver damage

- Contraindication: Asthma, marked bradycardia

- IV hydralazine (vasodilator) :

- Side effects: headache,nausea, vomitting, dizziness, flushing, tachycardia, palpitation & hypotension

- Because of hypotension preload with gelofusin adv.

- Contraindication- SLE, severe tachycardia & MI

# Magnesium Sulphate

- Clinical use: Prevention & treatment of seizure in eclampsia / severe pre eclampsia
- Dose: 4g IV stat then 1g/hr to be continued 24hr after last seizure
- Side effects: nausea,vomiting,flushing, drowsiness,confusion,loss of tendon reflexes, hypotension, decrease U/O, respiratory depression, arrhythmias,cardiac arrest
- Because of toxicity, Mg levels monitored

# Drugs in early pregnancy

- Mifepristone- 200mg PO
- Mechanism:

  Antiprogestogenic steroid

  Sensitizes myometrium to prostaglandin-induced contractions & ripens the cervix
- Clinical use:

  Medical termination of pregnancy

  Medical management of miscarriage/IUD
- Side effects: Gastro intestinal cramps, rash, urticaria, headache,dizziness,
- Contraindication: severe asthma

# Misoprostol

- Synthetic prostaglandin
- PO/PV route
- Clinical use:

  - Medical TOP

  - Medical management of miscarriage/ IUD

  ( For 1st trimester single dose of 400mcg

  From 12- 34 weeks 400mcg 3hrly ,max 5 doses)

  - Postpartum hemorrhage- 800mcg PR/PV

- Side effects: nausea,vomiting, diarrhoea, abdominal pain

# Methotrexate

- Cinical use: Medical management of ectopic pregnancy
- Dose 50mg per kg/m2
- Criteria- adenexal mass, non viable pregnancy hCG< 3000U, haemoperitonuem < 150ml
- Side effects:
- Disadvantage : repeated hCG levels, emergency surgery
- Advantage: Avoid surgery, tube preserved

# Menorrhagia / dysmenorrhea

- Mefenamic acid:
  - NSAID, reduces bleeding by 25%
  - Dose: 250-500mgx TDS  D1-3 of cycle or PRN
  - Side effects: Gastro-intestinal discomfort nausea, diarrhoea, bleeding/ulceration
- Tranexamic acid:
  - Antifibrinolytic,reduces bleeding by 50%
  - Dose: 1g TDS/QDS D1-4 of cycle
  - Contraindication: thromboembolic disease
  - Side effects: nausea,vomiting,diarrhoea, thrombo embolic event

# Progestogens

- Dysfunctional uterine bleeding/menorrhagia- ~~Norethisterone 5mg TDS D5-25 (3ks on/1wk off)~~
- Endometriosis- same dose contin. 9 months
- Menorrhagia- Depoprovera, Mirena
- Contraception- Mini pill, Mirena
- Induce withdrawal bleeding eg. PCOS ( 10 days Rx)
- Endometrial hyperplasia ( except atypical variety)- Depo provera, Mirena
- HRT
- Women with previous preterm labours -cyclogest pessary 200mg PV/PR daily till 36 weeks
- Following IVF/ICSI- Gestone inj + cyclogest pessary

# Estrogen

- Contraceptive - COC
- DUB/menorrhagia-COC
- Endometriosis- COC continued  for 9 months
- PCOS/Hirsutism - Dianette
- PMS- E2 patches + Mirena
- HRT
- Hypogonadism- cyclical therapy initially oestogen then  combined oestrogen & progesterone

# Gonadorelin analogue

- Mechanism- Initial stimulation then down regulation of GnRH receptors reducing the release of gonadotrophins and in-turn release of estrogen & androgen production

- Side effects:menopausal symptoms, headache, hypersensitivity( rash,asthma, anaphylaxis), palpitation,hypertension,breast tenderness & GI symptoms, irritation of nasal mucosa (spray)

- E.g Prostap, Zoladex & Buserelin spray
- S/C /IM inj. Monthly or nasal spray TDS for 6/12
- Maximum treatment no more than 6 months

# Gonadorelin analogue- clinical use

- Endometriosis
- Chronic pelvic pain
- Prior to myomectomy- size & bleeding
- Prior to hysterectomy for fibroids
- Infertility- pituitary desensitisation before induction of ovulation by gonadotrophin for IVF
- Menorrhagia in perimenopausal women
- Precocious puberty

# Danazol

- Mechanism: Inhibits pituitary gonadotrophin
  -antioestrogenic & antiprogestogenic
  - androgenic activity
- Dose : 200-800mg 4 divided dose for 3-6 month
- Clinical use:
  - Endometriosis
  - Benign fibrocystic disease(breast tenderness)
- Side effects: Nausea, headache,dizziness, weight gain, libido changes, androgenic side effects ( acne, oily skin, hair loss,voice changes)

# Anti-emetic Drugs in Pregnancy

More than 30 million women took Bendectin from 1956 to 1983. At least 25 epidemiological studies and 2 meta-analyses have been performed regarding its use during pregnancy, making it the **world's most studied drug in pregnancy**. ***Also one of the most talked about Litogen***

**Promethazine , Chlorpromazine, Diphenhydramine, Dimenhydrinate and Cyclizine** are safe but better avoided near term

**Ondansetron and Metoclopramide** should be used with caution, particularly during the

# Antihistaminics In Pregnancy

- First-generation (e.g. **chlorpheniramine)** and second-generation (e.g. **cetirizine**) antihistamines have not been incriminated as human teratogens.
- No controlled trials with loratadine and fexofenadine in human pregnancy

* H1 blockers do not increase the teratogenic risk in humans and may, in fact, be associated with a protective effect. By preventing vomiting, antihistamines may ensure better metabolic conditions to the fetus and thus may reduce some.

# Analgesics & Anti-inflammatory Drugs in Pregnancy

| Drugs/WkS. | 0-12 | 12-24 | 24-Term | Comments |
|---|---|---|---|---|
| Paracetamol | S | S | S | hepatic/renal tox. |
| Aspirin | C | C | N | closure of D.A.in utero |
| NSAID | S | C | N | ---do--- |
| " - Ketorolac | N | N | N | |
| Pethidine/ Dextrpropo/ Codeine/Pentazocine | - | - | C | withdrawl sympt. |

* S = Safe C = Cautious use N = Not to use

## NSAIDs In Pregnancy : COX 2 (Celecoxib) Inhibitors

In humans, an ↑ incidence of oligohydramnios has been observed in women who consumed significant amounts of aspirin, non-selective COX inhibitors or selective COX 2 inhibitors during the third trimester of pregnancy.

COX 2 inhibitors have been found to be nephrotoxic particularly during nephrogenesis (during last part of pregnancy and early neonatal period)

# Anxiolytic,Sedative & Hypnotic Drugs In Pregnancy

Benzodiazepine Drugs e.g.

~~Diazepam / Alprazolam - Category D~~

- Buspirone - Category B
- Zolpidem - Category B

# Antidepressants in Pregnancy

* Amitryptiline Category C
* Doxepin Category C
* Imipramine Category C
* Lithium Category D

- Sertraline Category B
- Citalopram Category B

# U.T.I. in pregnancy

dilated and kinked because of :

- increased progesterone relax smooth muscle
- obstruction of the lower ureters in late pregnancy

This encourages :

stasis and reflux of infected urine up the ureter and kidney

- ↑ bladder volume and ↓ bladder tone
- ↓ ureteral tone, contribute to ↑ urinary stasis and ureterovesical reflux

# U T I in Pregnancy :

- Asymptomatic bacteriuria ( colony count< $10^5$) :

Untreated , can lead to cystitis in 30% & pyelonephritis in 50%

- Acute cystitis : dysuria, urgency, frequency
- Acute pyelonephritis: fever, chills, nausea, vomiting and flank pain.

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Treating Asymptomatic Bacteriuria with Antibiotics

* clears bacteriuria
* ↓ incidence of Pyleonephritis
* ↓ incidence of premature delivery
* ↓ incidence of low birth weight baby

# U.T.I. in pregnancy

- Amoxicillin 500 mg. tds 7 days or

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- Cephalaxin 500 mg. tds 7 days or
- Nitrofurantoin 100 mg. tds 7 days or

$2^{nd}$ / $3^{rd}$ generation cephalosporins and Amoxy / Clavulinate can be given

Avoid Aminoglycosides / Quinolones

# Malaria In Pregnancy

Immuno suppression and loss of acquired immunity to malaria

- Placenta is the preferred site of sequestration and development of malarial parasite.
- atypical in presentation – Hypoglycemia
  - Acute pulmonary oedema
  - Acute renal failure
  - Anaemia
  - Convulsions / Coma

# Malaria In Pregnancy - Fetal complications

- Spontaneous abortion
- Pre mature birth, still birth
- Placental insufficiency
- I.U.G.R. (temporary / chronic)
- Low birth weight
- Fetal distress
- Trans placental spread of the infection to the fetus can result in congenital malaria.

# Drugs For Malaria In Pregnancy

*First trimester* : **Quinine + Clindamycin**

*2nd / 3rd trimester* : *above* + *Artemisin* +
**Mefloquine,**
**Pyrimethamine / sulfadoxine**
**(as required)**

*Contra indicated* : Tetracycline; Doxycycline;

Primaquine; Halofantrine

# Antiepileptic drugs (AED) in pregnancy

1. Optimise AED before conception
2. Monotherapy as far as possible
3. Discuss Teratogenic potential of AED & risk of major & minor birth defects
4. Pre- pregnancy & Pregnancy Folic acid (0.5 mg. daily) supplementation
5. Vit. K supplementation (10mg. Daily) or

   Inj. Vit. K as soon as after onset of labor

# Pregnancy , Epilepsy & Anti -Epileptic Drugs (AED)

**Consider No drug with seizure**

**v.**

**AED with its possible risks**

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**Congenital abnormalities if mothers taking AED :**

* hare lip or cleft palate,
* malformation of the limbs , heart, face, eyes and ears
* neural tube defects .

The risk of neural tube defects is

0.2 - 0.5 %. in the general population

1 % risk with carbamazepine

1 - 2 % with sodium valproate

# Antiepileptic drugs (AED) in pregnancy

## For Pts. On Carbamazepine & Valproate

* Alfa Feto Protein (AFP) level - at 14 - 16 Wks.

* USG - at 16 - 20 Wks.

* Amniocentesis for AFP & Acetylcholinesterase levels

# Antifungal Drugs In Pregnancy

- **Imidazoles -** safe as topical therapy for fungal skin infections . Nystatin is minimally absorbed and is effective for vaginal therapy
- **Amphotericin B -** no reports of teratogenesis
- **Fluconazole -** exhibits dose-dependent teratogenic effects; safe at lower doses (150 mg/day)
- **Ketoconazole, flucytosine, and griseofulvin - teratogenic** and/or embryotoxic in animals

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*Clinical Infectious Diseases, Vol. 27, pp. 1151-1160, Nov. 1998*

# Thyrotoxicosis During Pregnancy

**Graves' disease - important cause of maternal and fetal morbidity.**

* **Rx with mainly Thionamides or surgery ( for few )**
* **RAI is contraindicated**
* **Fetal goiter and hypothyroidism may be caused by excessive PTU or methimazole**
* **Dosage of antithyroid drugs is adjusted frequently , maintain the free hormone levels in the upper one third of the normal range.**
* **Pre-op. preparation with iodides is contraindicated for fear of neonatal goiter and hypothyroidism**
* **A high titers of TSI titers suggest the development of neonatal hyperthyroidism.**

# Toxoplasmosis In Pregnancy

Pregnant lady presenting with :-

* fever, chills, and sore throat,
* enlargement of the posterior cervical lymph nodes,
* malaise, fatigue, headaches, muscle aches,
* who is seronegative for mononucleosis,

**should be tested for toxoplasmosis infection**

Toxo - IgM & IgG should be ordered

# Toxoplasmosis In Pregnancy

SPIRAMYCIN from the first trimester until delivery

↓ the risk of fetal infection by 60%.

Presently, this drug is not known to have a teratogenic effect

Dose : 6 to 9 miu / day in divided doses.

[Rovamycin forte - 1tab.(3miu)]

Infection in fetus ( if confirmed) - Add pyrimethamine + leucovarin+ sulfadiazine

# Antirheumatic drug therapy in pregnancy

- Aspirin
- NSAIDs
- Corticosteroids
  Prednisone
  Dexamethasone

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- Hydroxychloroquine
- Sulfasalazine
- D-penicillamine

- Methotrexate
- Cyclosporin
- Azathioprine
- Chlorambucil
- Cyclophosphamide

# Rx of Bronchial Asthma in Pregnancy

Short acting ß agonist inhaler - safe

- Long acting ß agonist inhaler - not studied
- Inhaled Beclomethasone & Budesonide - safe
- Other inhaled steroids not tested
- Oral Prednisolone safe to fetus, ↑ maternal complications
- Emergency Rx - regular dose of ß agonist inhaler at

  15 - 20 minutes for 3 to 4 doses

- Add Ipratropium Inhalation

# Penicillins

- Collaborative Perinatal Project
- Frequency of congenital anomalies no greater than expected among children of 4,356 women treated with penicillin (or one of its derivatives) during 1st 4 lunar months of pregnancy

# Erythromycin

- Surveillance study of Michigan Medicaid recipients (1985-1992)
- No association between drug and congenital malformations in 6,972 newborns exposed during 1st trimester
- Avoid estolate form (cholestatic hepatitis)
- Less but reassuring data with clarithromycin and azithromycin

# Clindamycin

- Hungarian Case-Control Surveillance of Congenital Abnormalities (1980-1996)
- OR (95% CI) for clindamycin 1.2 (0.4-3.8) and for lincomycin 1.3 (0.3-5.1)
- Limited numbers

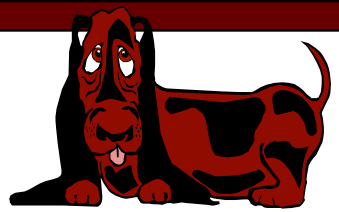
# Metronidazole

- Mutagenic in bacteria and carcinogenic in animals
- Small number of reports raised suspicion of teratogenic effect

# Metronidazole

- Outcome of interest = occurrence of birth defects in live - born infants
- Overall weighted OR during the 1st trimester calculated by meta-analysis of 7 studies was 0.93 (95% CI 0.73-1.18)

# Fluoroquinolones



- Arthropathy in weight-bearing joints of animals
- 200 women exposed to fluoroquinolones during pregnancy
- Rates of major malformations did not differ between groups exposed to quinolones during 1st trimester (2.2%) and control group (2.6%)
- Gross motor milestones did not differ between children in 2 groups

# Tetracycline

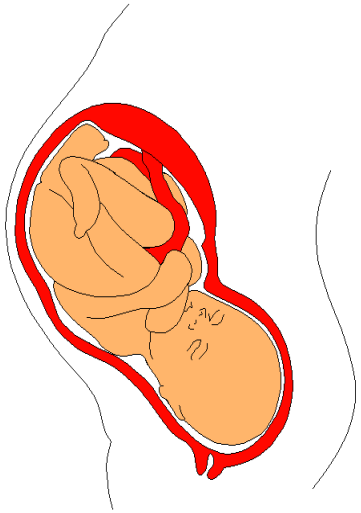
- Main risk is yellow-brown discoloration of teeth
- Risk only later than 4-5 months gestation when deciduous teeth begin to calcify
- No staining from doxycycline documented
- Effects on bone minimal

# Local Anesthetics - Lidocaine

- Considered relatively safe for use during pregnancy

# Epinephrine

- Potential to compromise uterine blood flow
- Studies have failed to demonstrate adverse fetal effects
- Low doses used in dentistry
- Avoid inadvertent intravascular injection

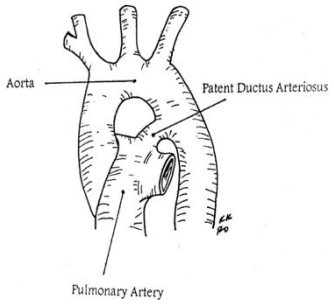


# Acetaminophen

- “Analgesic of choice”
- Occasional use at therapeutic doses
- Chronic use or overdose

# NSAIDS (including Aspirin)

- Increased risk of miscarriage
- Gastroschisis (abdominal wall defect)
- Avoid use during late pregnancy (3rd trimester)
  - ↑ Bleeding
  - Inhibition of prostaglandin synthesis
    - Prolonged labour
    - Constriction of ductus arteriosus

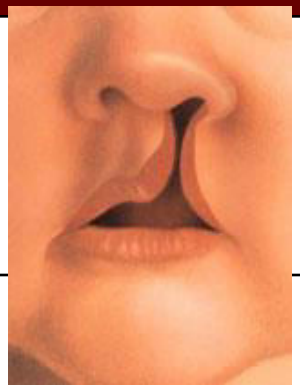


# Narcotics

## (Codeine, Oxycodone, etc.)

- Don’t appear to ↑ risk of birth defects
- Low dose short-term regimens acceptable
- Respiratory depression

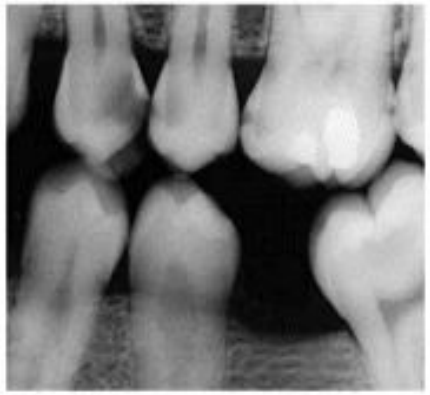
# Benzodiazepines



- Meta-analysis
- Cohort studies showed no association between fetal exposure to BZDs and risk for major malformations or oral cleft
- Case-control studies showed that risk for major malformations or oral cleft alone was increased.

# Radiation

- In most cases of diagnostic x-rays the fetal radiation exposure is much below the threshold dose of 5 to 10 rad



# Known Teratogens

- Alcohol (Ethanol)
- Carbamazepine
- Cytotoxic chemotherapy
- DES
- Isotretinoin and Etretinate
- Lithium
- Methimazole
- Misoprostol
- Phenytoin
- Thalidomide
- Trimethoprim
- Valproic Acid
- Warfarin

- Alcohol and tobacco in pregnancy probably cause more harm than all other drugs combined

# 1) Tobacco

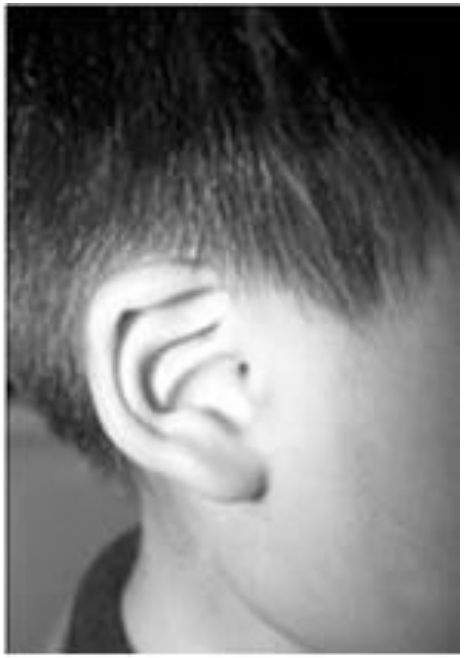
- No evidence it causes birth defects
- HOWEVER, increased risk of
  - spontaneous abortion
  - placental abruption
  - prematurity- 10% linked to smoking
  - low birth weight - causes 30% of LBW status
  - perinatal mortality increased by 40%
  - increased SIDS risk

# Smoking - neonatal effects

- More excitable, hypertonic and difficult to console
- Show more stress/abstinence signs
- Greater need for handling and poorer self-regulation
- Clear dose-response relationship

# 2) Alcohol

- Classic fetal alcohol syndrome is rare but nasty – dysmorphism, stunted growth and CNS defects



# 3) Opiates

- heroin & methadone main players
- no evidence they cause birth defects
- main fetal risks are
  - prematurity
  - poor fetal growth (IUGR)
  - NEONATAL ABSTINENCE SYNDROME

# Neonatal abstinence syndrome

- Occur in 60-90% of narcotic exposed babies
- onset - ~90% show signs by 72 hours
- differential diagnosis - low sugar etc.

# Signs of NAS

- Wakefulness
- Irritability
- Tremors
- Hyperactivity
- Diarrhea & vomiting
- Poor feeding and weight gain
- Sneezing

# NAS - management

- If severe – Rx of choice is MORPHINE
- Gradual withdrawal over 7-17 days
- Ideally infants should 'room-in' with mothers to:
  - reduce length of stay
  - reduce number taken into foster care
  - increase breastfeeding

# Outcome of NAS

- SIDS risk increased about 5 fold
- developmental outcome - conflicting results
  - most studies show normal intelligence
  - closely linked to family & social stability

# Maternal methadone & neonatal withdrawal

- Maternal methadone dose does not correlate with risk of NAS
- Therefore don't be stingy with methadone

**–Berghella, V. et al, Am J. Obs&Gyn, vol 189#2, Aug 2003**

# 4) Cocaine

- Increased SA, prematurity, IUGR and placental abruption
- No evidence of neonatal withdrawal
- Majority of studies show no or minimal effect on neurodevelopmental outcomes
- Some evidence of language delays in cocaine exposed infants
- Conclusion – *it's probably not good for you*

# SSRI and birth defects

- Conflicting data, but both Health Canada and US FDA issued warnings of a small increase in congenital heart defects (VSD) in mothers taking paroxetine (Paxil)
- Other SSRI/SNRI do not appear to carry significant risk of birth defects

# SSRIs and neonatal behaviour

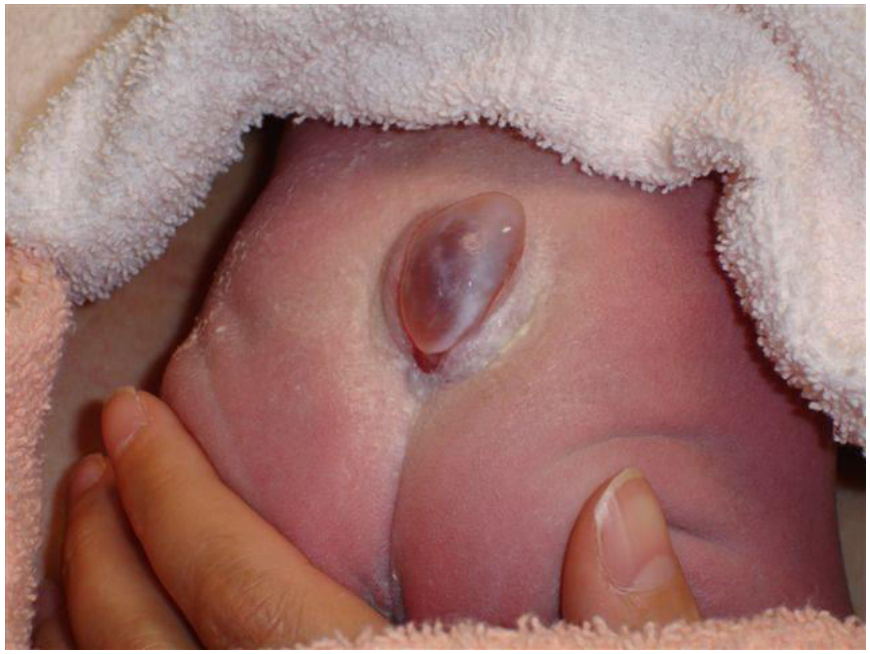
- Study from Israel
- 60 newborns with prolonged in utero exposure to SSRIs, with matched controls

# SSRI - other effects

- Exposure in the second half of pregnancy associated with increased risk of persistent pulmonary hypertension – a rare but potentially nasty problem
- Lower birthweight and increase in feeding difficulties

# 7) Valproic acid - antifolate

- associated with increased incidence of spina bifida – therefore avoid in pregnancy



# 7) NSAIDs

- Can cause premature closure of the ductus arteriosus
- Therefore avoid in pregnancy

# 9) Isoretinoin (Accutane)

- Causes very severe birth defects including facial dysmorphism, hearing and visual impairment and mental handicap in 25% of pregnancies
- Be VERY careful in prescribing this drug to females!
- Ensure negative pregnancy test 2 weeks before prescribing and use 2 forms of birth control

# 10) Tetracyclines & sulfonamides

- Avoid in pregnancy – tetracyclines discolour teeth

- Sulfonamides can displace bilirubin from albumin – avoid in 3rd trimester

# Magnesium Sulfate

- $MgSO_4$ used to treat seizures, ↑BP for ~75 years
  - Optimum dosing, concentration and therapeutic range undefined
  - Mg bound to proteins ~50%
    - Total vs Free in assays
  - Pk - One vs Two compartment – what does body do to drug
  - Pharmacodynamics – what does drug do to body - BP

# $MgSO_4$ Therapeutics

- 2-Compartment model most appropriate
- $[Mg^{++}]$ needs to be characterized
- Disease state alters disposition
- $[Mg^{++}]$ between 2 – 4 mmol/L produce more than half-maximal reduction in systolic & diastolic BP

# Penicillins

- Category B in pregnancy
  - Cross the placenta easily and rapidly
  - Concentrations equal maternal levels

- Lactation
  - Crosses in low concentrations
  - Compatible with breastfeeding

# Cephalosporins

- Category B in pregnancy
  - Cross the placenta during pregnancy
  - Some reports of increased anomalies with specific cephalosporins (cefaclor, cephalexin, cephradrine)
  - Primarily cardiac and oral cleft defects
- Lactation
  - Excreted into breastmilk in low concentrations
  - Considered compatible with breastfeeding

# Carbapenems
## (ertapenem, imipenem, meropenem)

- Category B/C/B in pregnancy
  - Likely cross the placenta
  - Very little human data
- Lactation
  - Excreted into breastmilk in low amounts
  - Unknown effects but likely low clinical significance

# Fluoroquinolones
## (floxins)

- Pregnancy Category C
  - Not recommended in pregnancy
  - Cartilage damage in animals
  - Safer alternatives usually exist
- Lactation
  - Excreted into breastmilk
  - Limited human data
  - AAP says compatible with breastfeeding

# Macrolides
(azithromycin, clarithromycin, erythromycin)

- Pregnancy Categories B/C/B
  - Cross the placenta in low amounts
  - Limited data with azithromycin and clarithromycin
- Lactation
  - Erythromycin compatible
  - Others probably compatible

# Aminoglycosides
## (amikacin, gentamicin, tobramycin)

- Pregnancy Category C
  - Rapidly cross placenta
  - Enter amniotic fluid through fetal circulation
- Lactation
  - Compatible with breastfeeding
  - Not absorbed through GI tract

# Sulfonamides

- Pregnancy Category C
  - Readily cross the placenta
  - Concerns of use at term
- Lactation
  - Excreted into breastmilk in low levels
  - Use should be avoided in premature infants

# Tetracyclines
## (doxycycline, minocycline, tetracycline)

- Pregnancy Category D
  - Can cause problems with teeth and bone and other defects/effects
  - Have been linked to maternal liver toxicity
- Lactation
  - Compatible with breastfeeding
  - Serum levels in infants undetectable

# Miscellaneous Antibiotics

- Aztreonam
  - Pregnancy Category B, likely safe in pregnancy, little human data
  - Lactation – Compatible per AAP
- Clindamycin
  - Pregnancy Category B, commonly used
  - Lactation – Compatible per AAP

# Miscellaneous Antibiotics

- Linezolid
  - Pregnancy Category C, no human data available
  - Lactation – unknown, myelosuppression in animals
- Metronidazole
  - Pregnancy Category B, carcinogenic in animals, avoid in 1st trimester if possible
  - Lactation – hold feeds for 12-24hrs afterward

# Miscellaneous Antibiotics

- Nitrofurantoin
  - Pregnancy Category B, possible hemolytic anemia with use at term
  - Lactation – Compatible, avoid with G-6-PD deficiency
- Trimethoprim
  - Pregnancy Category C, potentially problematic early in pregnancy
  - Lactation – Compatible as combination drug

# Miscellaneous Antibiotics

- Vancomycin
  - Pregnancy Category B, compatible
  - Lactation – likely compatible, not absorbed

# Antivirals
## (acyclovir, famciclovir, valacyclovir)

- Pregnancy Category B
  - Acyclovir and valacyclovir readily cross the placenta
  - Can be used for HSV treatment and suppression
- Lactation
  - Acyclovir and valacyclovir are compatible
  - Famciclovir should be avoided

# Antiretrovirals/NRTI
## (abacavir, didanosine (ddI), emtricitabine (FTC))

- Pregnancy Categories C/B/B
  - Maternal benefit usually outweighs fetal risk
  - Cross the placenta
  - Limited data with each do not show increased risk of anomalies
  - Didanosine has been associated with severe lactic acidosis w/ or w/o pancreatitis

# Antiretrovirals/NRTI (lamuvidine (3TC), stavudine (d4T))

- Pregnancy Category C
  - Maternal benefit usually outweighs fetal risk
  - Cross the placenta by simple diffusion
  - Data with lamivudine show no increased risk of anomalies
  - Stavudine has been associated with severe lactic acidosis w/ or w/o pancreatitis
  - All NRTIs have been possibly linked to mitochondrial dysfunction postnatally

# Antiretrovirals/NRTI (tenofivir, zalcitabine (ddC), zidovudine (AZT))

- Pregnancy Category B/C/C
  - Maternal benefit usually outweighs fetal risk
  - Cross the placenta by simple diffusion
  - Limited data with zalcitabine do not show increased risk of anomalies
  - Zidovudine is commonly used, but may cause neonatal anemia
  - Limited data with tenofivir show low risk of teratogenicity

# Antiretrovirals/NNRTI
## (delavirdine, efavirenz, nevirapine)

- Pregnancy Category C
  - Maternal risk usually outweighs fetal risk
  - Likely cross into fetus (nevirapine readily)
  - Delavirdine has possible VSD risk, but limited human data
  - Efavirenz is associated with anomalies in monkeys, limited human data, possible NTD
  - Nevirapine can cause hepatotoxicity and rash

# Antiretrovirals/PI

- Pregnancy Category B/C
  - Maternal benefit usually outweighs fetal risk
  - Likely cross the placenta
  - All PIs can cause hyperglycemia (⇧ GDM?)
  - Atazanavir can cause hyperbilirubinemia
  - Indinavir can cause nephrolithiasis

# Antiretrovirals/Fusion Inhibitor (enfuvirtide)

- Pregnancy Category B
  - Maternal benefit usually outweighs fetal risk
  - Very large molecule (4492 daltons), likely does not cross placenta
  - Animal data does not show risk
  - No human data available
  - Hold during first trimester if possible

# Antiretroviral Combinations

- Atripla (1 tab daily)
  - Efavirenz, emtricitabine, tenofovir
- Trizivir (1 tab BID)
  - Abacavir, lamivudine, zidovudine
- Combivir (1 tab BID)
  - Lamivudine, zidovudine
- Truvada (1 tab daily)
  - Emtricitabine, tenofovir
- Epzicom (1 tab daily)
  - Abacavir, lamivudine

# Antifungals/Azoles
## (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)

- Pregnancy Categories C/C/C/D
  - Likely cross placenta
  - Fluconazole $\geq$ 400mg/day seems to be associated with cranio-facial abnormalities
  - Itraconazole appears to have low risk
  - Ketoconazole can impair testosterone and cortisol synthesis
  - No data in humans is available for voriconazole, increased risk in animals

# Antifungals/Azoles
(fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)

- Lactation
  - Fluconazole is compatible per AAP
  - Itraconazole could concentrate in milk and body tissues, not recommended
  - Ketoconazole is compatible per AAP
  - No data with voriconazole, not recommended

# Antifungals/Echinocandins
## (anidulofungin, caspofungin, micafungin)

- Pregnancy Category C
  - No data with anidulofungin
  - No human data with caspofungin, single case at UVA, animal data suggests risk
- Lactation
  - No human data, but probably compatible

# Antifungals/Polyenes

- Amphotericin B
  - Pregnancy Category B, compatible, lipid complexes also compatible
  - Lactation – no data available

# Triptans (5-$HT_1$ agonists)

- Pregnancy Category C
  - Limited human data exists, sumatriptan has been associated with VSDs in several cases
  - No data available in humans for almotriptan, eletriptan, frovatriptan, or zolmitriptan
  - Limited human data exists with naratriptan and rizatriptan, although animal data indicates moderate risks
  - Pregnancy registry available for exposures

# Triptans (5-$HT_1$ agonists)

- Lactation
  - Cross into breastmilk and may concentrate
  - No reports of human lactation with almotriptan, frovotriptan, naratriptan, rizatriptan, or zolmitriptan
  - Sumatriptan is compatible per AAP
  - Eletriptan is likely compatible with low concentrations

# Ergots
## (Dihydroergotamine, ergotamine)

- Pregnancy Category X
  - Oxytocic properties could cause IUGR by vascular disruption or increased uterine tone
  - Early exposure appears safe, not teratogens
  - Chronic exposure is contraindicated

- Lactation
  - Contraindicated

# Butalbital and Caffeine

- Butalbital
  - Pregnancy Category C, can see neonatal withdrawal symptoms with long-term use
  - Lactation – not recommended
- Caffeine
  - Pregnancy Category B, doses generally lower than that in coffee
  - Lactation – compatible

# Dichloralphenazone and Isometheptene (Midrin)

- Dichloralphenazone
  - Pregnancy Category B
  - Lactation – similar agent considered compatible
- Isometheptene
  - Pregnancy Category C, extremely limited data
  - Lactation – potentially compatible

# DRUGS AFFECTING UTERINE MUSCLE CONTRACTILITY

# Oxytocin (Syntocinon)

- Octapeptide
- Strong rhythmical contraction of myometrium
- Large doses- sustained contraction(↓ placental blood flow & fetal hypoxia/death)
- Clinical use:

- IOL (IVI 3U syntocinon+50 ml of saline)

- Augment slow labour (IVI same as above)

-3rd stage of labour- 5 U IM for HTN ,cardiac disease

- IVI 40 U in 500ml saline ( PPH)

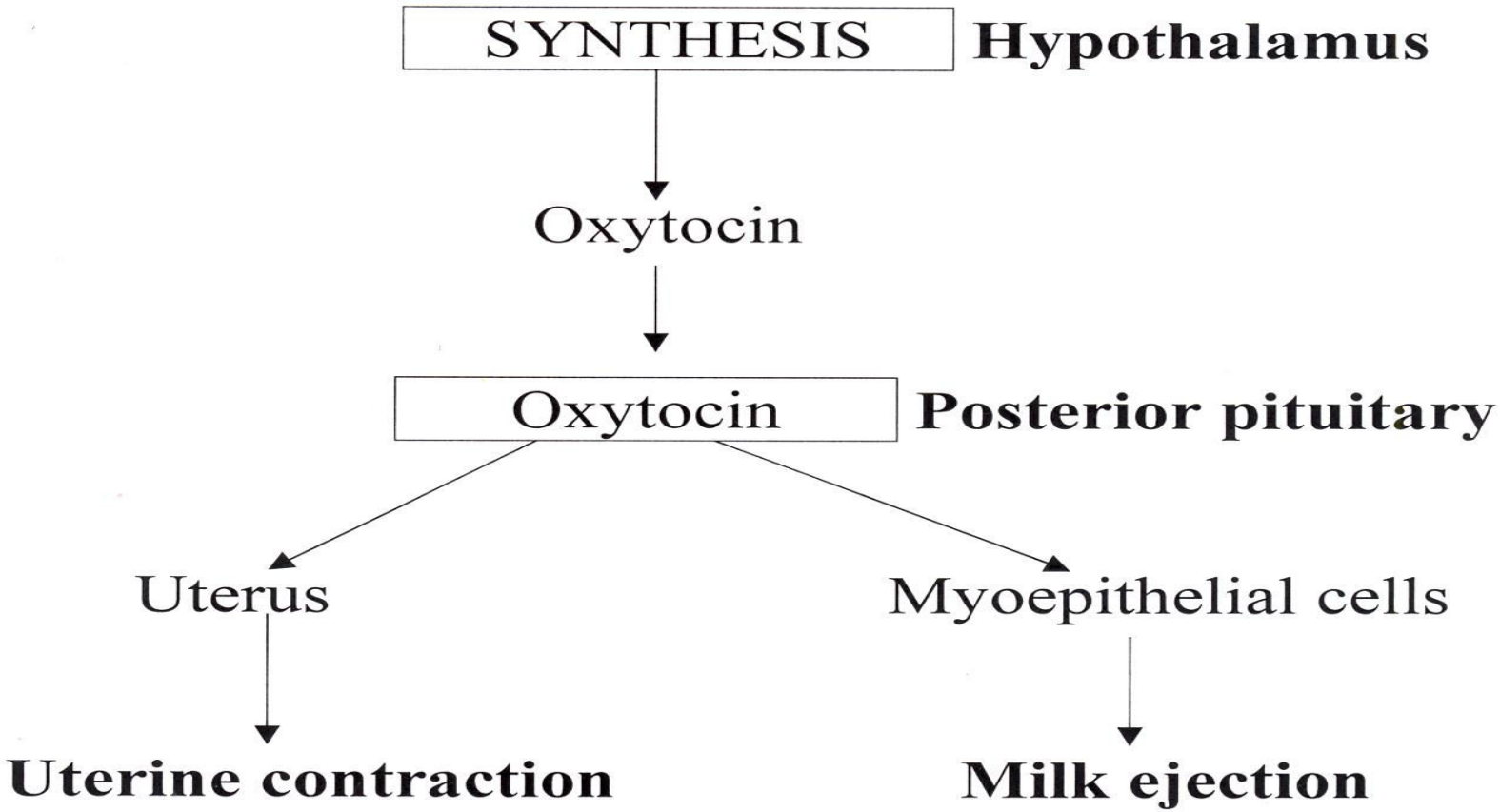
-Surgical termination of preg./ERPC- 5U slow IV

# OXYTOCIN (Syntocinon®)

## Synthesis

- **Is a posterior pituitary hormone secreted by the posterior pituitary gland.**
- **Oxytocin secretion occurs by sensory stimulation from cervix ,vagina , and from suckling at breast.**

# OXYTOCIN


SYNTHESIS
Hypothalamus
Oxytocin
Oxytocin
Posterior pituitary
Uterus
Myoepithelial cells
Uterine contraction
Milk ejection

# Pharmacokinetics of oxytocin

## Absorption ,Metabolism and Excretion

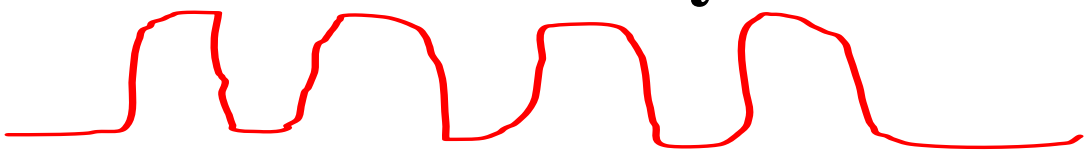
- Not effective orally
- Administered intravenously
- Also as nasal spray(impaired milk ejection)
- Not bound to plasma proteins
- Catabolized by liver & kidneys
- Half life = 5 minutes

# Role of oxytocin

## Uterus

- Stimulates both the frequency and force of uterine contractility particularly of the fundus segment of the uterus.

- These contractions resemble the normal physiological contractions of uterus (contractions followed by relaxation)



- **Immature uterus is resistant to oxytocin.**

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- **Contract uterine smooth muscle only at term.**

- **Sensitivity increases to 8 fold in last 9 weeks and 30 times in early labor.**

- **Clinically oxytocin is given only when uterine cervix is soft and dilated.**

# Mechanism of action

- **The interaction of endogenous or administered oxytocin , with myometrial cell membrane receptor promotes the influx of ca ++ from extra cellular fluid and from S.R in to the cell , this increase in cytoplasmic calcium ,stimulates uterine contraction .**

# Therapeutic Uses of Oxytocin

1. **Induction & augmentation of labor****

**(slow I.V infusion)**

a) **Mild preeclampsia**

b) **Uterine inertia**

c) **Incomplete abortion**

d) **Post maturity**

e) **Maternal diabetes**

# Therapeutic Uses of Oxytocin (continue)

2. **Post partum uterine hemorrhage**

   **(I.V drip)**

   **(ergometrine is often used)**

3. **Impaired milk ejection**

**One puff in each nostril 2-3 min before nursing**

## Side Effects:

1. **Maternal death due to:**

   a) **Hypertension**

   b) **Uterine rupture**

   c) **Fetal death(ischaemia)**

2) **Water intoxication**

# Ergometrine

- Sustained myometrial contraction & vasoconstriction
- Syntometrine IM:

5U syntocinon(rhythmic contraction in 2min) +

500µg ergometrine(sustained contraction in 7 min)

- Side effects – Nausea, vomiting, abdominal pain, chest pain, palpitation, severe HTN , Stroke & MI
- Contraindication- HTN, Cardiac disease
- Clinical use:

- Management of 3rd stage
- Management of PPH - 2nd dose give. Alternatively IV ergometrine can be given (works with in 40 sec)

# Ergot Alkaloids

- Ergometrine (Ergonovine)
- Methylergonovine

# Effects on the Uterus

- **Alkaloid derivatives induce TETANIC CONTRACTION of uterus without relaxation in between(not like normal physiological contractions)**

- **It causes contractions of uterus as a whole i.e. fundus and cervix(tend to compress rather than to expel the fetus)**

**Difference between oxytocin & ergots??**

# Clinical uses

- **Post partum hemorrhage (3rd stage of labor)****

**When to give it?**

## Preparations

**Syntometrine(ergometrine 0.5 mg + oxytocin 5.0 I.U), I.M.**

# Side effects

a) Nausea, vomiting, diarrhea

b) Hypertension

b) Vasoconstriction of peripheral blood vessels ( toes & fingers)

c) Gangrene

- **Contraindications:**

**1) Induction of labour**

---

**a) 1st and 2nd stage of labor**

**b) vascular disease**

**c) Severe hepatic and renal impairment**

**d) Severe hypertension**

# PROSTAGLANDINS (PGE2 & PGF2α)

## Therapeutic uses

1. **Induction of abortion (pathological)****
2. **Induction of labor (fetal death in utero)**
3. **Postpartum hemorrhage**

## Side Effects

a) Nausea , vomiting
b) Abdominal pain
c) Diarrhea
d) Bronchospasm (PGF2α)
e) Flushing (PGE2)

- **Contraindications:**
  a) Mechanical obstruction of delivery
  b) Fetal distress
  c) Predisposition to uterine rupture

- **Precautions:**
  a) Asthma
  b) Multiple pregnancy
  c) Glaucoma
  d) Uterine rupture

# Difference between PGS and Oxytocin:

- **PGS contract uterine smooth muscle not only at term(as with oxytocin), but throughout pregnancy.**
- **PGS soften the cervix; whereas oxytocin does not.**
- **PGS have longer duration of action than oxytocin.**

# Difference B/w Oxytocin and Prostaglandins

| Character | Oxytocin | Prostaglandins |
|---|---|---|
| Contraction | Only at term | Contraction through out pregnancy |
| | | |
| Cervix | Does not soften the cervix | soften the cervix |

# Difference (cont'd)

| Character | Oxytocin | Prostaglandins |
|---|---|---|
| **Duration of action** | **Shorter** | **Longer** |
| **uses** | **Induce and augment labour and post partum hemorrhage** | **Induce abortion in 2nd trimester of pregnancy.**<br><br>**Used as vaginal suppository for induction of labor** |

# Difference b/w Oxytocin and Ergometrine

| Character | Oxytocin | Ergometrine |
|---|---|---|
| Contractions | Resembles normal physiological contractions | Tetanic contraction ; doesn't resemble normal physiological contractions |
| Uses | To induce &augment labor.<br>*Post partum hemorrhage | Only in p.partum hemorrhage |
| Onset and Duration | Rapid onset<br>Shorter duration of action | Moderate onset<br>Long duration of action |

# Dinoprostone ( prostin E2)

- Vaginal **pessary**/gel
- Clinical use: IOL – 3mg 6hrs apart ( no more than 2 pessaries in 24hrs and max. 3 doses)
- Side effect: Nausea ,vomiting, diarrhoea, fever, Uterine hyperstimulation , HTN, bronchospasm
- Advantages :

- Mobile patient

-Reduce need for syntocinon

# Carboprost ( Hemabate)

- Dose ; 250µg deep IM repeated every 15 min max 8 doses.

  (OR Intra-myometrial use at C/S)

- Side effects: Nausea ,vomiting, diarrhoea, fever, bronchospasm, dyspnoea, pulmonary oedema, HTN, cardiovascular collapse

- Clinical use: Postpartum haemorrhage

# Atosiban(Tractocile)

- Oxytocin receptor antagonist
- ~~Inhibition of uncomplicated preterm labour~~ between 24-33 weeks ( Tocolytic)
- Contraindication: severe PET, eclampsia, IUGR, IUD, placenta previa, placental abruption, abnormal CTG, SROM after 30/40
- Side effects: Nausea,vomiting,headache, hot flushes, tachycardia, hypotension & hyperglycemia
- Dose- Stat IVI then continue infusion until no contraction for 6 hrs.

# Other tocolytics

- Salbutamol inhaler- 100 mcg x 2 puffs stat
- Terbutaline- 250 mcg subcutaneous

- Clinical use: both drugs are used for short term.

  (i) relaxing uterus at C/S

  (ii) ECV procedure

- Side effects: Headache, palpitation, tachycardia, MI ,arrhythmias, hypotension & collapse

# Nifedipine

- Calcium Channel blocker

- Clinical use:
- Mild to moderate- 5-20 mg TDS/PO
- Severe HTN- 10 mg Retard/PO
- Tocolytic- Incremental doses every 20 min until contraction stop, then 20 mg TDS/PO

- Side effects: Headache,dizziness,palpitation, tachycardia, hypotension,sweating & syncope.

# Mild /Moderate HTN/PET

- Methyldopa:

  -Dose: 250mg BD/TDS , PO max dose 3g /day

  -Side effects: Headache,dizziness,dry mouth , postural hypotension,nightmares, mild psychosis, depression,hepatitis & jaundice

  - Important to stop drug in postnatal period

- Labetolol 100-200mg BD/TDS PO max 2.4g/24hr

- ACE inhibitors are contraindicated in pregnancy

# UTERINE RELAXANTS

# DRUGS PRODUCING UTERINE RELAXATION( Tocolytic Drugs ).

## Action and Uses

**Relax the uterus and arrest threatened abortion or delay premature labor.**

### 1. β-ADRENOCEPTOR AGONISTS**

**Ritodrine, i.v. drip**

**Selective $\beta_2$ receptor agonist used specifically as a uterine relaxant.**

# β- adrenoceptor agonists

- **Mechanism of action**

**Bind to β-adrenoceptors , activate enzyme Adenylate cyclase , increase in the level of cAMP reducing intracellular calcium level.**

- **Side effects:**
- **Tremor**
- **Nausea , vomiting**
- **Flushing**
- **Sweating**
- **Tachycardia (high dose)**
- **Hypotension**
- **Hyperglycemia**
- **Hypokalaemia**

# 2.CALCIUM CHANNEL BLOCKERS

## e.g., Nifedipine

- **Causes relaxation of myometrium**
- **Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions**

## Unwanted effects

- Headache, dizziness
- Hypotension
- Flushing
- Constipation
- Ankle edema
- Coughing
- Wheezing
- Tachycardia

# 3. Prostaglandin synthetase inhibitors

- **The depletion of prostaglandins prevents stimulation of uterus**

**NSAID's e.g. Indomethacin**

**Aspirin**

**Ibuprofen**

# Adverse effects

**ulceration**

- **premature closure of ductus arterious.**

## 1. Association Between Stillbirth and Illicit Drug Use and Smoking During Pregnancy
## Varner, Michael W. MD

- To compare illicit drug and smoking use in pregnancies with and without stillbirth.

- For 663 stillbirth deliveries, 418 (63%) had cord homogenate and 579 (87%) had maternal cotinine assays performed. For 1,932 live birth deliveries, 1,050 (54%) had cord homogenate toxicology and 1,545 (80%) had maternal cotinine assays performed.

- Cannabis use, smoking, illicit drug use, and apparent exposure to second-hand smoke, separately or in combination, during pregnancy were associated with an increased risk of stillbirth. Because cannabis use may be increasing with increased legalization, the relevance of these findings may increase as well.


THANK
YOU