Pregnancy and Surgery- Do they mix?

Michael Rieker, DNP, CRNA, FAAN
Director, Nurse Anesthesia Program
Wake Forest Baptist Health

Case Presentation

You are working in the preadmission area and your next preop is a healthy 35 yo female pediatrician who is scheduled for an inguinal hernia repair as an outpatient. She informs you she is 8 weeks pregnant and is concerned about potential detrimental effects of surgery and anesthesia on the fetus. What now?

Surgery During Pregnancy: How Frequent?

- Swedish health-care registries: 0.75% or 5,405 out of 720,000 pregnancies
  - Mazze. *Am J Obstet Gynecol 1989;161:1178-85*
- US range is 1-2%
- In US involves over 80,000 anesthetics each year

Kuczkowski, K. (2006) The safety of anaesthetics in pregnant women. *Expert Opinion on Drug Safety*. 5(2):251-264.

How many times don't you even know?

- INCIDENCE OF SURGERY PRIOR TO KNOWING OF PREGNANCY

Most Common Surgeries in Pregnant Patients

- Appendectomy
- Cholecystectomy
- Adnexal disease
- Breast biopsy
- Cervical cerclage
- Ovarian cystectomy
- Trauma
- Intrauterine fetal surgery or exchange transfusion
- Neurosurgery
  - Nossek E. Ekstein M. Rimon E. Kupferminc MJ. Ram Z. *Acta Neurochirurgica*. 2011;153(9):1727-35.

Important physiologic changes

- Airway
- Mild hypervent/alkalosis
- Prone to aspiration
- Sensitive to drugs
- Anemia, increased CO
- Benign leukocytosis
- Hypercoagulable

Rates of complications

- Maternal death rate: .006%
- Miscarriage rate: 5.8%
- Premature labor: 3.5%
- Major birth defects with 1st trim. Surgery: 3.9%

- Cohen-Kerem R. Railton C. Oren D. Lishner M. Koren G. Pregnancy outcome following non-obstetric surgical intervention. American Journal of Surgery. 190(3):467-73, 2005 Sep. UI: 16105538

FETAL HAZARDS

- Exposure to teratogenic drugs
- Risk of intraoperative hypoxemia secondary to reduced UBF
- Risk of preterm delivery

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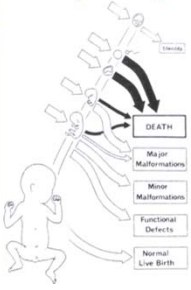
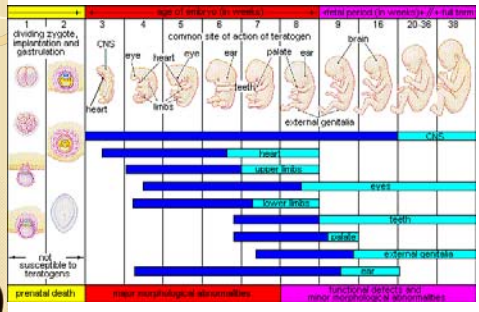
Principles of Teratology

- The susceptibility of an embryo depends upon the developmental stage at which the agent is applied
- Each teratogenic agent acts in a specific way on a particular aspect of cellular metabolism
- The genotype influences to a greater or lesser degree an animal's reaction to a teratogenic agent
- An agent capable of causing malformation may also cause an increase in embryonic mortality
- A teratogenic agent may not be deleterious to the maternal organism (but may be)

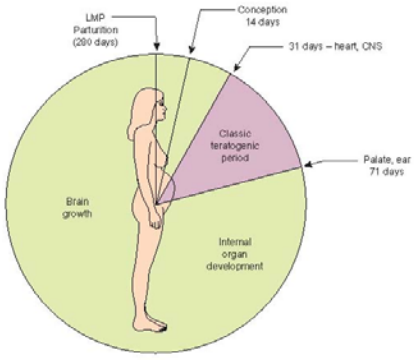
Fetal Development: Period of High Susceptibility



- Period of greatest concern begins at 15-18 days when organogenesis begins
- Reaches a peak at 30 days postconception
- Susceptibility decreases until days 55-60 and becomes minimal through day 90



Implications for anesthetizing women of child-bearing age…



General approach

- Virtually all drugs cross to some degree
- We really don't know much about what a given drug can or cannot do
- Use any drug only when necessary, when risk/benefit indicates, and then only in minimal effective dose

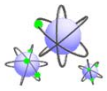
Maternal/Fetal Transfer

- Maternal/Fetal blood flow
- Placental binding
- Maternal, Placental,& Fetal metabolism
- Diffusion capacity
- Maternal & Fetal protein binding
- Maternal Dose/Drug Uptake

Placental drug transfer

- Depends upon:
  - Physical and chemical properties of drug
  - Characteristics of maternal, fetal, and placental circulations
  - Anatomy and physiology of the placenta

PLACENTAL TRANSPORT



- Molecular weight
- Lipid solubility
- Ionization
- Concentration gradient
- Protein binding
- Changes in maternal physiology
- Route of delivery

Documented Teratogens

ACE Inhibitors	Mercury
Alcohol	Phenytoin
Androgens	PPIs (some evidence)
Antithyroid drugs	Radiation (>5 rad)
Carbamazepine	Streptomycin/kanamycin
Chemotherapy agents	Isotretinoin (Accutane)
Cocaine	Tetracycline
Coumadin	Thalidomide
Diethylstibestrol	Trimethadione
Lead	Valproic acid
Lithium	Vit A derivatives (Retinoic acid)

United States FDA Category Ratings of Drugs During Pregnancy

- **Category A: Controlled studies demonstrate no risk.**
- **Category B: No evidence of risks in humans.**
- **Category C: Risk cannot be ruled out.**
- **Category D: Potential evidence of risk.**
- **Category X: Contraindicated in pregnancy.**

United States FDA Category Ratings of Specific Anesthetic Agents

Anesthetic Agent	Classification
Induction Agents	
Etomidate	C
Ketamine	B
Methohexital	B
Propofol	B
Thiopental	C
Inhaled Agents	
Desflurane	B
Halothane	C
Isoflurane	C
Sevoflurane	B

United States FDA Category Ratings of Specific Anesthetic Agents (cont.)

Anesthetic Agent	Classification
Local Anesthetics	
2-Chloroprocaine	C
Bupivacaine	C
Lidocaine	B
Ropivacaine	B
Tetracaine	B
Opioids	
Alfentanil	C
Fentanyl	C
Sufentanil	C
Meperidine	C
Morphine	C

United States FDA Category Ratings of Specific Anesthetic Agents (cont.)

Anesthetic Agent	Classification
NMBD	
Atracurium	C
Cisatracurium	B
Curare	C
Mivacurium	C
Pancuronium	C
Rocuronium	C
Succinylcholine	C
Vecuronium	C
Benzodiazepines	
Diazepam	D
Midazolam	D

Teratogenic Effects of Anesthetics

- Probably minimal to nonexistent and have never been conclusively demonstrated
- Drugs most common are N_2O and benzodiazepines
- N_2O probably teratogenic in animals because of reduced UBF; this can be prevented by addition of a halogenated agent
- Inhalational agents, narcotics, intravenous agents, local anesthetics have a long history of safety when used during pregnancy

Teratogenicity

- NO anesthetic agent (except cocaine) in normal clinical doses has been PROVEN to be teratogenic in humans.
- No anesthetic agent has been PROVEN to induce preterm labor and/or delivery

Inhalation agents

Lipid solubility promotes transfer

- Duration of exposure relates to APGAR
- Iso, nitrous: F/M 0.7 even with short exposure
- Oxygen

Do volatiles harm the baby in utero?

- 50 women- GA with ½ MAC Des/Sevo compared with epidural
- No difference in APGAR or neurobehavioral scores

- The Maternal and Neonatal Effects of the Volatile Anaesthetic Agents Desflurane and Sevoflurane in Caesarean Section: a Prospective, Randomized Clinical Study Karaman, S.; Akercan, F.; Aldemir, O.; Terek, M.C.; Yalaz, M.; Firat, V. The Journal of International Medical Research, 34 (2) 2006, pp. 183-192

Nitrous oxide concerns

- Oxidizes cobalt atom on Vit B12
- Inhibits methionine synthetase and tetrahydrofolate
- Concern for DNA production
- Demyelination with long-term exposure

IV inductions

- Thiopental, methohexital, ketamine achieve F/M around 1.0
- Propofol and etomidate: lower F/M then pentothal (0.6)
- One study = lower APGARs with prop.
- Good for hypotension, better at preventing awareness

Package Insert-Benzodiazepines

"An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be appraised of potential risk to fetus."

Opioids

- Morphine, demerol, sufenta, stadol, nubain cross readily and achieve > 50% fetal concentration
- Protein-binding limits transfer- fent and alfenta stay < 0.5
- Remi crosses to high conc, but little evidence of neonatal effects
- Spinal/epidural route does not preclude fetal transfer

Local Anesthetics

- Readily cross placenta.
- Controversy regarding fetal/neonatal effects
- Most conclusive: cause "transient, minor neurobehavioral effects"

Muscle relaxants

- Ionized drugs- little transfer
- Sux shows up in UV only after large doses
- NDMRs have F/M < 0.15

Anticholinergics/ Anticholinesterases

- Atropine
- Scopolamine
- Glycopyrrolate
- Neostigmine
- What would standard neostig/robinul reversal do?

Antihypertensives

- β-blockers- No
- Clonidine/methyldopa: OK
- Hydralazine: choice drug
- SNP: lipid soluble- rapidly crosses
- ACE inhibitors- No

Vasopressors

- Concern for uterine vasoconstriction
- Ephedrine mainstay
- Phenylephrine gaining acceptance for safety in moderate doses, and without unwanted tachycardia

Antiasthmatic drugs

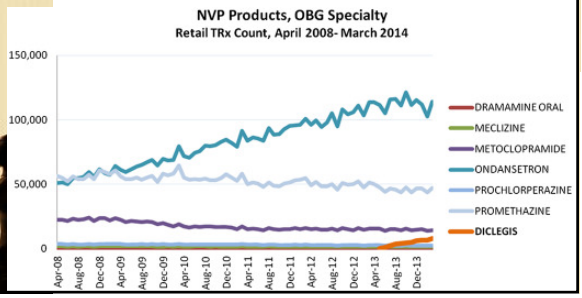
- Theophylline: safe (class C)
- Terbutaline
- Isoproterenol, metaproterenol: insignificant systemic absorption when inhaled. IV use may dec UBF
- Cromolyn: OK
- Steroids

Anticoagulants

- Warfarin- causes fetal loss or chondrodysplasia
- Avoided in 1st trim, but most switch to heparin throughout pregnancy

Antiepileptics

- Magnesium Sulfate
- Phenytoin (Dilantin)
- Phenobarbital
- Carbamazepine (Tegretol)



Antiemetics

- Ondansetron

Significant findings re: cleft palate

Odds ratios of cleft palate in offspring exposed to selected medications in the first trimester among women with first trimester nausea and vomiting of pregnancy, National Birth Defects Prevention Study 10/97–12/04

	Exposed		Unexposed		Crude		Adjusted[b]	
Medication Exposure[a]	Cases	Controls	Cases	Controls	OR	95% CI	OR	95% CI
Prokinetetics	5	18	520	3991	2.13	0.79–5.77	2.36	0.85–6.55
Metoclopramide	5	18	520	3991	2.13	0.79–5.77	2.36	0.85–6.55
5HT3 antagonists	11	46	514	3963	1.84	0.95–3.58	2.29	1.14–4.58
Ondansetron	11	44	514	3965	1.93	0.99–3.76	2.37	1.18–4.76
Antacids	21	198	504	3811	0.80	0.51–1.27	0.70	0.44–1.12
Calcium Carbonate	16	153	509	3856	0.89	0.47–1.34	0.69	0.40–1.17
Proton Pump Inhibitors	5	13	520	3996	2.96	1.05–8.32	2.59	0.88–7.63

Conflicting data

- Danish registry covering from1997-2010 (897,018 pregnant women). In contrast to earlier studies from same registry, found a 2-fold increased risk of cardiac malformations with ondansetron (odds ratio 2.0; 95% confidence interval 1.3–3.1), leading to an overall 30% increased risk of major congenital malformations. To rule out confounding by indication, also examined metoclopramide taken for morning sickness, detecting no increase in teratogenic risk.
- Andersen, J.T., Jimmenez-Solem, E., and Andersen, N.L. Ondansetron use in early pregnancy and the risk of congenital malformations. Int Soc Pharmacoepidemiol. 2013;

Odds ratios of hypospadias in offspring exposed to selected medications in the first trimester among women with first trimester nausea and vomiting of pregnancy
National Birth Defects Prevention Study 10/97–12/04

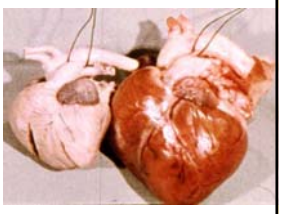
	Exposed		Unexposed		Crude		Adjusted[b]	
Medication Exposure[a]	Cases	Controls	Cases	Controls	OR	95% CI	OR	95% CI
Antihistamine Antiemetics	26	107	629	1849	0.71	0.46–1.11	0.68	0.43–1.09
Promethazine	21	78	634	1878	0.80	0.49–1.30	0.78	0.46–1.31
Other Antihistamine	19	54	636	1902	1.05	0.62–1.79	1.05	0.59–1.85
Diphenhydramine	11	37	644	1919	0.89	0.45–1.75	1.00	0.49–2.07
Cetirizine	8	17	647	1939	1.41	0.61–3.28	1.12	0.44–2.84
Prokinetetics	6	9	649	1947	2.00	0.71–5.65	1.17	0.39–3.55
Metoclopramide	6	9	649	1947	2.00	0.71–5.65	1.17	0.39–3.55
5HT3 antagonists	5	19	650	1937	0.78	0.29–2.11	0.55	0.19–1.53
Ondansetron	5	18	650	1938	0.83	0.31–2.24	0.57	0.20–1.60
Emetrol/Coke syrup	6	15	649	1941	1.20	0.46–3.10	1.05	0.38–2.87
Phosphorated Carbohydrate Solution	5	15	650	1941	1.00	0.36–2.75	0.94	0.32–2.72
Antacids	40	90	615	1866	1.35	0.92–1.98	0.66	0.43–1.02
Calcium Carbonate	34	68	621	1888	1.52	1.00–2.32	0.73	0.45–1.18
H2 Blockers	7	15	648	1941	1.40	0.57–3.44	1.07	0.41–2.83
Ranitidine	4	11	651	1945	1.09	0.34–3.42	0.70	0.20–2.41
Proton Pump Inhibitors	7	5	648	1951	4.22	1.33–13.33	4.36	1.21–15.81
Pyridoxine	8	48	647	1908	0.49	0.23–1.04	0.56	0.25–1.24
Steroids	10	8	645	1948	3.78	1.48–9.61	2.87	1.03–7.97

Antibiotics

- Penicillins, cephalosporins, EES: OK
- Sulfonamides: compete with bili for albumin binding
- Tetracycline: OK, except for teeth
- Aminoglycosides

Analgesics

- Aspirin
- Acetaminophen
- Propoxyphene
- Codeine



Teratogenicity of Anesthetic Agents

- Maternal hemodynamic changes more critical than specific agents in most cases
- Avoid at all costs **maternal HYPOXIA, HYPOTENSION, HYPERCARBIA, HYPERTHERMIA**

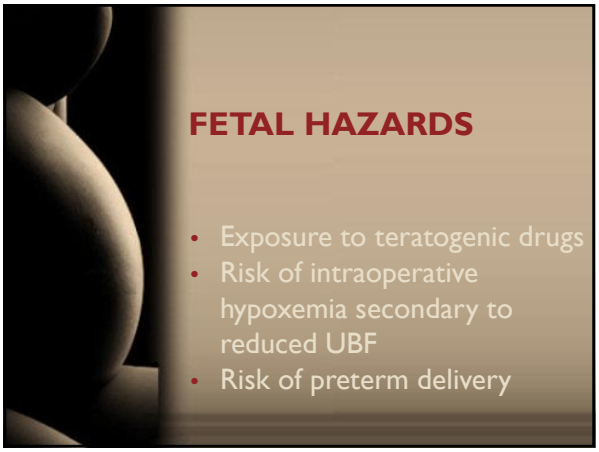
"All things are poison and nothing is without poison, only the dose permits something not to be poisonous."
~Paracelcus

- "Because it is clear that virtually every drug and every inhalation anesthetic are teratogenic to some species under certain conditions, there is no "best" anesthetic agent."

Kuczkowski, K. "Nonobstetric surgery in the parturient: anesthetic considerations". *Journal of Clinical Anesthesia (2006) 28, 5-7*

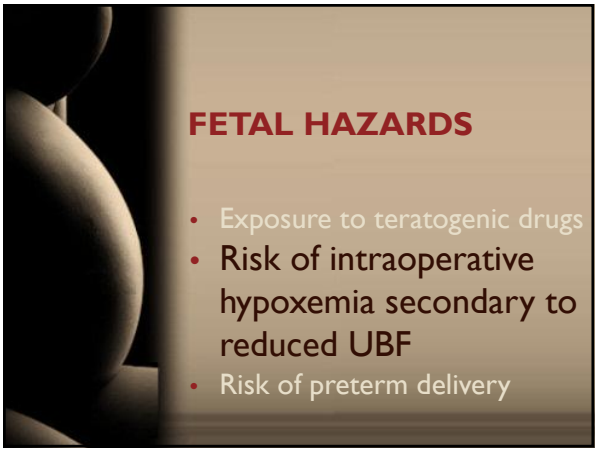
RECOMMENDATIONS

- Use drugs with a long history of safe clinical use
- Document apgar scores



FETAL HAZARDS

- Exposure to teratogenic drugs
- Risk of intraoperative hypoxemia secondary to reduced UBF
- Risk of preterm delivery



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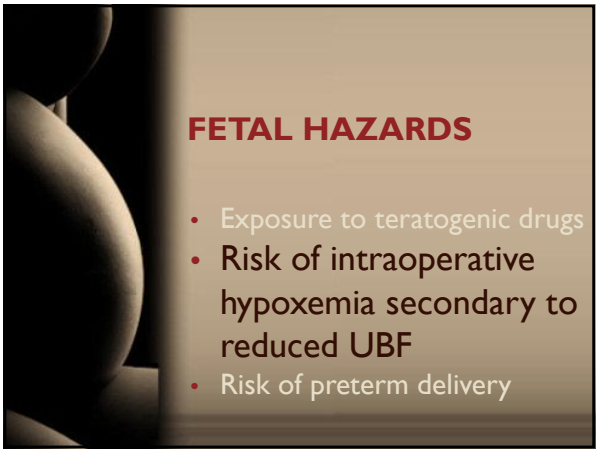

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UTERINE BLOOD FLOW

$$\frac{\text{uterine arterial pressure} - \text{uterine venous pressure}}{\text{uterine vascular resistance}}$$

Systemic hypotension
Supine hypotension
Vasopressors
Sick placentas
Uterine tone

Hypotension

- Hypovolemia, anesthetics, aortocaval compression
- IV bolus, but careful of pulm edema

Laparoscopy

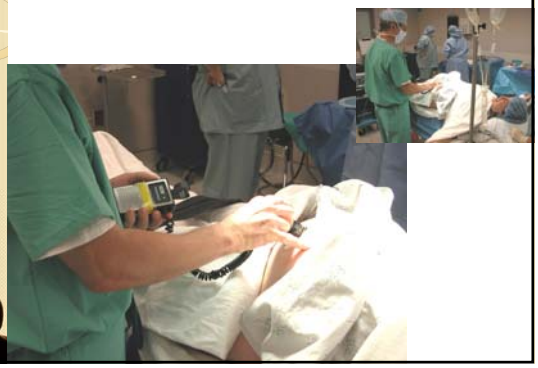
- Left uterine displacement
- maintaining ETCO2 32-34 mmHg
- maternal BP within 20% of baseline
- Limit insufflation pressure to 12-15 mmHg

- O'Rourke N. Kodali BS. **Laparoscopic surgery during pregnancy.** *Current Opinion in Anaesthesiology. 19(3):254-9, 2006 Jun.*

What about EFM?

- Can obtain FHR after about 18 wks
- Variability begins ~25 weeks
- Should use after 22-24 wks
- "What are you going to do differently?"

Management of Anesthesia for the Pregnant Surgical Patient



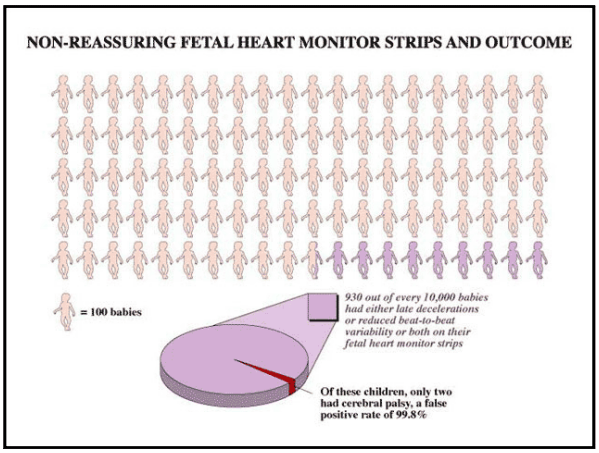
Severe Fetal Bradycardia in a Pregnant Surgical Patient Despite Normal Oxygenation and Blood Pressure

- Some obstetricians believe fetus would not be compromised as long as maternal oxygenation, circulation normal
- 27 yo, 34 week gestation; FHR < 70 bpm with normal maternal hemodynamics
- Emergency section; Apgar 1, 5, 7

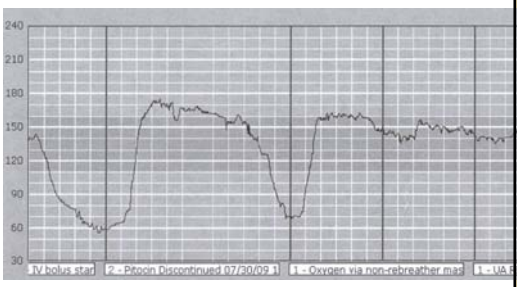
Ong BY et al: *Can J Anesth* 50(922):2003

Arguments Against Routine EFM

- Anesthesia has been associated with predictable changes in FHR that does not result in fetal mortality
- Continuous EFM could lead to the false impressions of fetal distress with maternal-fetal harm
- Continuous EFM has not been clearly shown to prevent poor fetal outcomes
- EFM is impractical for many urgent/emergent procedures
- Interpretation of continuous EFM requires experience not common to OR personnel



Management of FHR Abnormalities:



Perioperative Management

- Preoperative Assessment
  - Should include pregnancy testing if diagnosis in doubt; mandatory testing is controversial
  - Date of LMP should be documented on anesthetic record in any female between age 12-50
  - Offer testing if more than 3 weeks from LMP or if patient requests
- If Pregnant
  - Premedicate to reduce anxiety, catechols, impact UBF
  - Consider aspiration prophylaxis
  - Discuss perioperative tocolysis with obstetrician

Principles for Anesthetic Management of the Parturient <24 Weeks Gestation

- Postpone surgery until second trimester, if possible
- Request preoperative assessment by an obstetrician
- Counsel the patient preoperatively
- Use a nonparticulate antacid as aspiration prophylaxis
- Monitor and maintain oxygenation, normocarbia, normotension, normothermia, and euglycemia
- Use regional anesthesia when appropriate
- Avoid N_2O in high concentrations during general anesthesia?
- Document fetal heart tones before and after the procedure

Principles for Anesthetic Management of the Parturient >24 Weeks Gestation

- Counsel the patient preoperatively
- Discuss use of prophylactic tocolytic agents with the obstetrician
- aspiration prophylaxis
- Glucocorticoids 24-48 hours pre-op (24-34 weeks gestation)
- Maintain left uterine displacement pre-, intra-, and postoperatively
- Monitor and maintain oxygenation, normocarbia, normotension, normothermia, and euglycemia
- Use fetal monitoring intraoperatively when possible to optimize the intrauterine environment; monitor for uterine contractions postoperatively

Practical Points

- Never sacrifice maternal safety
- If feasible, regional anesthesia preferable
- No evidence of any anesthetic technique better than another as long as maternal oxygenation, perfusion maintained
- Uterine displacement essential beyond 20 weeks
- Use pharmacologic aspiration prophylaxis, RSI, cricoid pressure
- Secure airway quickly as oxygen levels fall quickly
- Maintain maternal glucose above 70 mg/dL

Practical Points

- Avoid BNZ
- Keep inhalation agents below 1 MAC to prevent decreased maternal CO
- Be aware of reduced drug requirements for regional or general anesthesia
- Minimize stimulation of uterine contractions by appropriate anesthetic techniques, optimal surgical conditions, cautious reversal, tocolytics if indicated

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Does exposure to anesthetics increase the risk of spontaneous abortion?

Allaert SE. et. Al. *Acta Anaesthesiologica Belgica.* 2007;58(2):119-23.

Mazze RI, Kallen B. *Reproductive outcome after anaesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol 1989;161:1178-85*

Do we cause it?

- Hong. Adnexal mass surgery and anesthesia during pregnancy: a 10-year retrospective review.
  Int J Obstet Anesth. 2006 Jul;15(3):212-6.

Preterm labor

- We don't specifically treat preventatively
- Maintain homeostasis

Postoperative Management

- Monitor FHR, uterine activity
- Maintain maternal monitoring
- Left uterine displacement
- Manage preterm labor aggressively
  - Indomethacin
  - Magnesium sulfate
  - Terbutaline

Postoperative Management

- Chance of spont Ab only in first week. After that risk is no higher than normal
- Toco useful, as analgesics may mask awareness of contractions
- Pain may encourage premature labor
- Hypercoagulable

Drugs used during lactation

Drugs used during lactation

- Passage goes back to Fick's principle
- Amount in breast milk is a fraction of blood level and usually has no or negligible effects on neonate
- Some drugs are concentrated in milk

Anesthetic drug transfer into breast milk

- 0.005% (range, 0.002%-0.013%) of the maternal midazolam dose
- 0.027% (0.004%-0.082%) of the propofol dose
- 0.033% (0.006%-0.073%) of the fentanyl dose
- represent averages of 0.009%, 0.025%, and 0.039% of the respective elimination clearances.

- Nitsun M. Szokol JW. Saleh HJ. Murphy GS. Vender JS. Luong L. Raikoff K. Avram MJ. **Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk.** *Clinical Pharmacology & Therapeutics. 79(6):549-57, 2006 Jun.*

Cautions

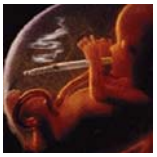
- Toxic drugs are never acceptable
- Neonatal allergies
- Like most things, inadequate controlled studies of outcomes
- Reduced maternal or infant ability to metabolize drug may concentrate it

General principles

- Post-partum, colostrum mostly. Little drug excreted
- Time administration to follow feeding
- Avoid long-acting drugs

American Academy of Pediatrics

- Drugs whose effects are unknown, but may be a concern:
  - Psychotropics
  - Metronidazole
- Drugs that are contraindicated:
  - Marijuana
  - Phencyclidine
  - Nicotine
  - Cocaine
  - Heroin
  - Amphetamines



Drugs usually compatible with breast feeding

- Opioids, sedatives, anticonvulsants
- No obvious adverse effects
- Breast milk has only 1-2% of maternal conc
- Lipid sol like valium or barbs may cross to a greater extent, and elimination is slow

American Academy of Pediatrics

- Drugs and lactation database (LactMed)

http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

Drugs and Breast feeding

- Decide if drug therapy is really necessary
- Use the safest drug
- Consider monitoring drug concentrations
- Minimize exposure: feed before dosing

What 8 things can I do today?

- Review changes of pregnancy
- Postpone case; at least until after 1st trimester
- Avoid supine position after 24 weeks
- Carefully approach airway- RSI after 1st trim.
- Select drugs with good safety record; use regional when possible
- Assess FHR a & p if > 24 weeks.
- Modest doses of almost any typical drugs will be OK
- Avoid hypotension, keep slightly hypocarbic