IN SUMMARY
TERMINATION OF PREGNANCY

PREGNANCY TERMINATION TECHNOLOGY

Introduction

- *1973: Roe v. Wade; Trimester Approach*
- *Number of Abortions Stable or Decreasing*
- *~ 1/3 of Women 15-44 Undergo Abortion*
- *Abortion 10-11x Safer than Continuing Pregnancy, 2x Safer than PCN Injection*
- *91% 1st TM, 9% 2nd TM, .01% 3rd TM*
- *1965: Illegal Ab = 17% of Maternal Deaths*

Termination of Pregnancy

- *Practiced since antiquity*
- *Many societies accept this practice,*
- *Some reject it,*
- *Even considered it a crime.*
- *Most widely used method early in the first trimester is surgical*
  - *Vacuum aspiration*
  - *Safer and less painful than dilation and curettage*
- *Estimated 26 million pregnancies are terminated legally each year throughout the world*
- *20 million are terminated illegally*
  - *More than 78,000 deaths*
- *United States, legal - performed by trained personnel rate of death from surgical termination of pregnancy is 0.6 per 100,000 women*
- *Serious morbidity less than 1 percent*
- *Abortion*
  - *Lack of information on contraception*
  - *Fear the side effects of contraceptive methods*
  - *Often considered when contraception fails*
  - *Countries where contraceptives not widely available.*
- *Abortion services are not always readily available.*
- *United States has one of the highest abortion rates among developed countries*
- *1995 approximately 86 percent of U.S. counties no abortion providers or facilities*

Incidence of First Trimester Ab

- *Most common surgical procedure*
- *Maximum increase occurred between 1972 and 1980*
- *During 1980's rate remained stable*
- *1990 – 1.4 million legal abortions reported*
- *Since 1990 they have decreased by 2-4% per year*
- *1994 – under 1.3 million*
- *Probably an underestimate*
- *CDC figures about 15% less than private sources*
- *Most women are young white and unmarried*
- *Half performed before the eighth week*
- *Five of six in the first trimester*
- *Young women obtain Ab later than older women*
- *90% obtain Ab in their own states*
- *Diagnosis and recognition of pregnancy*
  - *Delays start of prenatal care*
  - *Increases risk of complications*
  - *Limits options of abortion methods*

Methods of Abortion

Techniques

- *Pharmacologic*
  - *Saline*
  - *Other hypertonic agents*
  - *Prostagalndins*
  - *Phospholipids*
  - *Sertotonin and MAO inhibitors*
  - *Pastes*
  - *Systemic toxins*
- *Mechanical*
  - *Extra amniotic fluids*
  - *Bougies & metreurynter*
  - *Supercoils*
  - *Suction D&E*
- *Hysterotomy*

Primitive Attempts

- *Horseback riding & violent excercise*
- *Sitz baths*
- *Coitus*
- *Boxing with blows to abdomen*
- *Electrical stimulation*
- *Potassium permanganate*
- *Air insufflation*
  - *Mouth*
  - *pump*

Foreign Body Method

- *Catheter – soft – rigid (stylet)*
- *Knitting needles*
- *Coat hanger*
- *Screw driver*
- *Curtain rod*
- *Umbrella ribs*
- *Wires*
- *Paint brushes*
- *Chopsticks*
- *Toothbrushes*
- *Goosequills*
- *“abortion machine”*

Douches

- *Nozzle flush with the vagina*
- *Nozzle into the cervix*
- *Nozzle into the posterior fornix*
- *Soap*
  - *Peritonitis*
  - *Emboli*
  - *Hemolysis*
- *Turpentine*
- *Pine oil*
- *Hydrogen peroxide*

Curettage Techniques

- *Use of aspiration dates back to Russian physician first reported in 1927*
- *Chinese 1958*
- *Widespread in europe in 1960's*
- *U.S. since 1970*

Mechanical Techniques

- *Metreurynter*
  - *Described by Manabe in 1969*
  - *Dilate cervix to 12 to 16 Hegar*
  - *Rubber balloon tipped device similar to Foley*
  - *Inflate with 200-300 cc saline*
  - *Weights of 300-800 grams attached and hung from end of bed*
  - *Oxytocin given*
  - *Antibiotics given*
  - *Laminaria tents speed up process*

Mechanical Techniques

- *Bougies – elastic GU rods .5 to 1 cm diameter, 30-40 cm long*
- *One or two inserted extra-ovularly*
- *Ends cut off*
- *Oxytocin infusion given*
- *Removed when labor established*
- *#8-10 Hegar dilator needed to insert*
- *31 hours mean time to abort*
- *Live fetus*

Supercoils

- *First appeared in USA May 1972 in Philadelphia health dept report*
- *Originated by L.A. psychologist*
- *Reported only in lay press*
- *20 women transported to Philadelphia from Midwest hotel*
- *Coils inserted and women shipped back to hotel to abort*

Pastes

- *Developed in Germany in 1930's*
- *Interruptin*
  - *Composite of various ethereal oils such as crocus, aloe, eucalyptus, camphor, iodine, thmol*
  - *Mixed with soaps, olive oil, cocoa butter*
  - *Given through undilated cervix*
  - *If no labor in 24 hours then oxytocin 15-50 units given IM or buccal*

  - *By 1932 there were 25 fatalities*

Urea Instillation

- *80 grams in 150 cc 5% Dextrose*
- *100-250 cc fluid removed*
- *166 or 332 mu/min oxytocin*
- *Diazepam or meperidine*
- *71/74 aborted*
- *Mean time 18.2 hours*
- *BUN rose to 33*
- *WBC increased, fibrinogen drop, FDP's rise, platelets drop*

Extra-amaniotic Solutions

- *Widely used in japan*
- *Extra-ovular catheter inserted and various fluids instilled*
- *30-50 cc Rivanol (disinfectant)*
  - *96% abortion rate - Manabe*
  - *95% abortion rate – Nabriski*
- *Japanese reported on toxic effects of saline and found no advantage*
- *Glucose used as well*

Mechanism of Saline Abortion

- *Spontaneous increase in contractions in 1-2 hours*
- *Increased oxytocin sensitivity*
- *E_2, E_3, P and HCG all fall within 3 hours of injection*
- *Intrauterine volume increases 26% in 3 hours*
- *Na concentration reaches 900-3400 meq/l*
- *Osmolarity increases from 270 mOsm/l to 1980-3960*
- *Mothers Hct falls 10%*
- *Serum N_a peaks at 2-4 hours*
- *Coagulation changes occur rapidly*
  - *Platelets fall*
  - *Fibrinogen falls below 100 mg%*
  - *FDP's in urine in 98%*

Saline Instillation

- *Most widely used until early 80's for 12-28 weeks*
- *Also used for dead fetus evacuation*
- *Difficult before 14 weeks*
  - *Pelvic location of uterus*
  - *Membranes fuse to wall after 16 weeks*
  - *No ultrasound available*
- *100-200 cc 20% NaCl*
- *Times*
  - *Average to abort 34.5 hours*
  - *>72 hours in 11-14%*
  - *>1 week in 5%*

Saline Instillation

- *Time to abort*
  - *Unrelated to gravidity*
  - *Unrelated to age of patient*
  - *Unrelated to gestational age*
  - *Unrelated to amount of saline*

Complications of Saline AB

- *Fever and infection – 2 to 16%*
  - *Pyrogens ?*
  - *Staph, coliforms, diphtheroids. Strep*
- *Hemorrhage (w or w/o DIC) – 4%*
- *Coagulopathy*
- *Siezures*
  - *Headaches, thirst, water intoxication*
- *Peritoneal spillage – peritonitis*
- *Bladder injection*
- *Intramyometrial injection – necrosis*
- *Rh isoimmunization (transplacental hemorrhage)*

Surgical Techniques

- *≤ 14 Weeks:*
  - *Suction Curettage*
  - *Medical Abortion (≤ 56 days LMP)*
- *14-24 Weeks and Beyond:*
  - *Dilatation and Evacuation (D+E)*
  - *Intact D+E ("D+X")* {evacuation/extraction*}*
  - *Labor Induction Methods (Prostaglandins)*
  - *Amnioinfusion (HS, Urea, Prostaglandins)*

Cervical Dilatation

- *Mechanical:*
  - *Done at Time of D+E*
  - *Convenient for Patient*
  - *May be Uncomfortable*
  - *Increased Risk of Perforation (Compared with Osmotic Dilators)*
- *Osmotic Dilators (e.g. Laminaria)*
  - *Increased Time, Inconvenience*
  - *Less Pain, Decreases Perforation Risk*
- *Examples:*
  - *Laminaria japonicum, L. digitatum*
  - *Dilapan*
  - *Lamicel*

Laminaria

- *Hydroscopic seaweeds*
  - Laminaria digitata
  - Laminaria japonicum
- *Gamma radiation*
  - *Does not kill spores*
- *Various sizes*
  - *Strings*
  - *Collar*

Laminaria

- *Inserted 3-6 hours prior to surgery*
- *May be up to one day*
- *Past internal os*
- *Usually results in at least 8 mm dilation*
- *Direct dehydrating effect on cervix*
- *Provoke release of prostaglandins*
- *1/2 fold decrease in cervical lacerations*

Suction Curettage

- *Office, Clinic or Hospital Setting*
- *Local (Paracervical Block) or IV Sedation*
- *General Anaesthesia Increases Risk*
- *Prophylactic Doxycycline Decreases Endometriitis Risk*
- *Rigid or Osmotic Dilators Used*
- *"No-Touch" Technique*

Dilatation and Evacuation

- *Avoid Mechanical Dilatation if Feasible*
- *Requires Additional Experience and Training*
- *Safer than Amnioinfusion in Most Cases when Performed by Experienced Operator*
- *Less Emotionally Traumatic for Most Patients (Compared With Labor Induction)*

Complications

- *Bleeding*
- *Infection*
- *Retained POC*
- *"Missed Abortion"*
- *Perforation – low risk, high risk variants*
- *Hematometra ("postabortal," or "re-do" syndrome)*
- *Undiagnosed Ectopic Pregnancy*

Menstrual Regulation

- *Aspiration up to 50 days LMP*
  - *Menstrual extraction*
  - *Menstrual aspiration*
  - *Menstrual induction*
  - *Minisuction*
- *Extremely safe*
  - *4-6 mm Karman cannula*

- *Foot or hand pumps*
- *Syringes*

Menstrual Regulation

3.9 % major complication rate

- *Hypotension*
- *Fever*
- *Cervical lacerations*
- *Acute infection*
- *Anesthesia reactions*
- *Uterine perforation*
- *Excessive blood loss*

- *Immediate about 0.85%*
- *Most delayed*
  - *Failed procedures*
  - *Infections*
  - *Ectopic pregnancy (undiagnosed)*
- *Often performed w/o documentation of pregnancy*
- *Prior to 1979 pregnancy test was positive only > 6 weeks LMP*
- *No need to know*
  - *In a study of 500 cases only 65% pregnant*
- *Paracervical or no anesthesia*
- *Rotates and scrapes*
  - *1-10 minutes*
  - *Sensation of bare endometrium, bubbles*

Possible Inhibitors of Myometrial Contractility

- *Progesterone*
- *Prostacyclin*
- *Relaxin*
- *Nitric oxide*
- *Parathyroid hormone-related peptide*
- *Corticotropin-releasing hormone*
- *Human placental lactogen*
- *Calcitonin gene-related peptide*
- *Adrenomedullin*
- *Vasoactive intestinal peptide*

Stimulators of Contractility

- *Increased of contraction-associated proteins*
  - *Myometrial receptors for prostaglandins*
  - *Myometrial receptors for oxytocin),*
- *Activation of certain ion channels*
  - *Increase in connexin 43*
- *Increase in gap junctions*
  - *Electrical synchrony*
  - *Allows effective* coordination *of contractions.*
- *Stimulated to contract by the actions of*
  - *Oxytocin*
  - *Stimulatory prostaglandins E(2)) and F(2)(alpha)).*

Initiation of Parturition

- *Fetus is in control in most viviparous animals*
- *Sheep and cow fetus triggers labor*
- *Human placenta lacks glucocorticoid-inducible enzyme 17(alpha)-hydroxylase-17,20-lyase*
- *Regardless final pathway for labor* ends in the uterus
- *Characterized by the development of regular phasic uterine contractions*

Initiation of Parturition

- *Myometrial contractions mediated through the ATP-dependent binding of myosin to actin*
- *Myometrial cells are sparsely innervated*
  - *become even less so during pregnancy.*
- *Regulation of the contractile mechanism largely humoral*
- *Parturition cascade at term*
- *Removes the mechanisms maintaining uterine quiescence*
- *Recruits factors promoting uterine activity*
- *Multiple positive-feedback loops*

Initiation of Parturition

- *Series of changes within the myometrium, decidua, and cervix*
- *Occurs over a period of* days to weeks
- *Synthesis and release of prostaglandins within the uterus*
- *Formation of myometrial gap junctions*
- *Activation of myometrial oxytocin receptors*
- *Endocrine, paracrine, and autocrine factors*
  - *switch in the pattern of myometrial activity from irregular contractures to regular contractions*

Physiologic Actions of Drugs Inducing Abortion

- *Implantation of a fertilized ovum (embryo)*
- *Complex interactions with the endometrium.*
- *Embryo becomes* attached *to the endometrial epithelium*
- Invades *the endometrial stroma on day 6 to 10 after ovulation.*
- *Depends on progesterone which*
  - *Modifies the transcription of many genes involved implantation process*
  - *Inhibits myometrial contractions*
- *Drugs used to terminate pregnancy*
  - *Inhibiting synthesis of progesterone,*
  - *Inducing myometrial contractions,*
  - *Antagonizing the action of progesterone*
  - *Inhibiting the development of the trophoblast.*

TERMINATION OF PREGNANCY

Role of Progesterone

- *Progesterone binds to its receptor*
- *Complex forms a dimer and binds to a segment of the promoter region of different target genes*
- *This genomic effect leads to changes in the structure of epithelial-cell membranes*
- *Synthesis of implantation proteins*
- *Progesterone decreases uterine contraction, probably by a genomic effect.*
- *In contrast, during labor, oxytocin and prostaglandins induce uterine contraction.*
- *Prostaglandins and oxytocin bind to their respective receptors*
  - *Increased phospholipase C activity*
  - *Increased intracellular inositol triphosphate (IP(3))*
  - *Increased calcium*
- *The released calcium interacts with myosin light-chain kinase (MLCK) on the contractile filaments to cause uterine contraction.*
- *Progesterone also exhibits nongenomic action by binding to oxytocin receptor and inhibiting the action of oxytocin*
- *During a normal pregnancy blastocyst attaches to the receptive endometrium, or decidua, on day 6 or 7 after ovulation.*
- *The trophoblast then traverses adjacent cells and invades the endometrial stroma.*
- *The agents used to terminate pregnancy are*
  - *Methotrexate - which inhibits trophoblast division*
  - *Prostaglandins -which increase muscle contraction*
  - *Epostane - decreases progesterone synthesis*
- *Mifepristone - progesterone antagonist*
  - *blocks the binding of progesterone to its receptor*
  - *amplifies the action of prostaglandins on the myometrium*
  - *induces cervical softening*

Oral Agents

- *Ergot*
- *Quinine*
- *Strychnine*
- *Whiskey*
- *Turpentine*
- *Phosphorus*
- *Castor oil*
- *Rosemary, nutmeg, aloe, cloves, thyme*
- *Spanish fly*
- *Arsenic, copper, lead, mercury*
- *Folate antagonists*

Prostaglandins

- *Mifepristone*
- *Misoprostol*
- *Gemeprost*

METHOTREXATE

- *50 mg/sq meter body surface IM*
- *800 ug misoprostol vaginally 3 to 7 days later*
- *Tylenol and codeine for cramps*
- *Return 1 week after misoprotol*
- *If beta hCG not 50% less then offer D&C*
- *Cytotoxic drug used to Rx ectopic and moles*
- *Lethal to trophoblast by blocking folic acid in fetal cells so they cannot divide*
- *Used with misoprostol it is 95% effective*
- *Several protocols are in use*

Inhibition of Progesterone Synthesis

- *Modified steroidal molecules*
  - *(2(alpha),4(alpha),5(alpha),17(beta))-4,5-epoxy-17-hydroxy-4,17-dimethyl-3-oxoandrostane-2-carbonitrile (**epostane**)*
  - *Block at receptor*
- *Inhibitors of ovarian and placental 3(beta)-hydroxysteroid dehydrogenase,*
  - *(**trilostane**)*
  - *Inhibit synthesis of progesterone from its precursor, pregnenolone.*
- *Action of epostane in reducing progesterone synthesis and terminating pregnancy is prevented by the administration of progesterone.*

Anti-Progesterones

- *First progesterone antagonist (antiprogestin) to be developed was **mifepristone***
- *Known as RU 486 or RU 38486*
  - *binds to the progesterone receptor with an affinity five times as great as that of progesterone*
- *Also inhibits transcription resulting in the down-regulation of progesterone-dependent genes*
  - *Decidual necrosis and detachment of the products of conception.*
  - *Endometrial blood vessels, causing damage that further compromises the embryo.*
- *Directly promote uterine contractions*
  - *Increasing myometrial-cell excitability*
  - *Cause cervical dilation.*

Epostane

- *Epostane given alone or in combination with prostaglandin E(2))*
- *Terminate pregnancies of less than 56 days' duration*
- *A dose of 200 mg must be given every six or eight hours for seven days*
- *Epostane caused nausea in 86 percent of women*
- *Success rate of only 84 percent*
- *Currently **not** used for this purpose.*

Prostaglandins

- *Natural prostaglandins - unstable,*
- *Lack specificity, and are poorly tolerated*
- *parenteral prostaglandin analogue sulprostone discontinued - associated with cardiovascular complications - acute myocardial infarction and severe hypotension*
- *Synthetic prostaglandin E(1)) compounds currently used are misoprostol and gemeprost*
- *Misoprostol is inexpensive, can be stored at room temperature, and is available in many countries for the treatment and prevention of peptic ulcer caused by nonsteroidal anti-*

inflammatory drugs.

Prostaglandin Side Effects

- *Dose related*
- *Fever*
- *Chills*
- *Gastrointestinal*
- *Lactation*
- *Bronchospasm*
- *Pre-treatment with Lomotil/Compazine*

Efficacy of Prostaglandins

- *Oral doses of misoprostol ranging from 400 to 3200 micrograms induce abortion in only 4 to 11 percent of women with pregnancies of 56 days' duration or less.*
- *Bioavailability is greater when the drug is administered vaginally and higher success rates have been reported with vaginal administration.*
- *Results with doses ranging from 800 to 2400 micrograms vary considerably*
  - *Rates of complete abortion of 22, 47, 61, and 94 percent have been reported.*
  - *Differences not related to the dose of misoprostol or the duration of gestation*

Side Effects of Prostaglandins

- *High incidence of side effects*
  - *Pain, dizziness, nausea, vomiting, diarrhea, chills, and rashes.*
  - *Fifty-three percent of women given 5 mg of gemeprost required opiate analgesia, as compared with 16 percent given 3 mg*
  - *Women receiving more than 3 mg of gemeprost frequently had to remain in the hospital overnight*
- *Misoprostol failures*
  - *Scalp or skull defects, cranial-nerve palsies, and limb defects such as talipes equinovarus*
- *The increase in uterine pressure related to uterine contractions or vascular spasm may be the cause*

MIFEPRISTONE

- *19-norsteroid*
- *AFFINITY*
  - *progesterone receptor - strong*
  - *glucocorticoid receptors - strong*
  - *androgen receptors – less*
- *Stimulates synthesis of PG by decidua*
- *Available*
  - *France*
  - *United kingdom*
  - *Sweden*
  - *China*
- *1980 compound synthesized at Roussel-Uclaf (hence **RU**-486)*
- *Became available in France soon thereafter*
- *Teutch (1975) studied how small chemical alterations in steroid molecules affected ability to bind*
  - *Developed a method of synthesizing versions of steroids that did not exist in nature*
  - *Alain Belanger (post-doc) the produced the molecules*
- *Initial effort was to produce a gluco-corticoid antagonist to aid wound healing*

- *Most potent was RU-38486 which was also found to block progesterone*
- *Teutsch*
- *Belanger – postdoctoral fellow*
- *Deraedt – progesterone binder as well*
- *Sakiz – corp. exec. Created formal project*
- *Barton – Nobel Laureate chemist*
- *Philibert – supvr. Of RU-486 project*
- *Hodgden – East Va med Sc. – TAB in monkey*
- *Bailieu & Hermann (Geneva) – TAB in humans*

Timetable

- *1950 – Aminopterin (folate antagonist used to produce medically indicated abortions*
- *1972 – PGE2 and PGF2α induced abortion (intolerable side effects)*
- *1975 – Selective prostaglandin analogs (still had side effects)*
- *1980 – More stable analogs (gemeprost {PGE1 methyl ester}, sulprostone {16- phenoxyl-tetranor-PGE2})*
- *1982 – Etienne-Emile Baulieu investigated glucocorticoid blockers and discovered RU-486 (mifepristone)*
- *1985 – Addition of prostaglandin aided in expulsion*
- *1988 – Licensed in France*
- *1993 - Methotrexate*

Rationale for Use of Mifepristone

- *Progesterone needed to sustain early pregnancy*
- *W/o progesterone uterus expels pregnancy*
- *Through prostaglandin mediated mechanism*
- *Epostane (3β-hydroxysteroid dehydrogenase inhibitor) prevents synthesis of progesterone {dosing every 6 hours for many days)*
- *Mifepristone binds the receptor with equal affinity as progesterone without activation*
- *Alters endometrium by affecting the capillary endothelium of the decidua (trophoblast separates and bleeding ensues)*
- *Also affects the tissues of the cervix*

MIFEPRISTONE

- *Most effective in early pregnancy*
- *7 weeks or less LMP have 95% rate*
- *9 weeks have 80%rate*
- *No good studies above 9 weeks*
- *Similar to miscarriage*
- *Use narcotics rather than NSAIDS*
- *1% need curretage*
- *.1% need transfusion*

MIFEPRISTONE

- *Three visits*
  - *600 mg mifepristone (5% expel)*
  - *400 ug cytotec orally 48 hours later*
  - *Return in 2 weeks for checkup*
  - *Dose not yet established (200 to 600 ug)*
- *600 mg orally*

- *36-48 hours later give a prostaglandin analog*
  - *Gemeprost transvaginally*
  - *Sulprostone IM*
  - *Misoprostol PO (400 ug)*
- *Earlier PG analogs unstable at room temp*
- *Misoprotol (Cytotec) used for treatment of ulcers*
- *Second dose may be given if no abortion*
- *Currently people are using 200 mg mifepristone and 800 ug misoprotol for 56 days with complete abortion rates of 97%*

Methotrexate and Prostaglandins

- *Methotrexate and misoprostol very effective in terminating pregnancy*
- *Dose of 50 mg per square meter of body surface*
- *Intramuscular injection*
- *Oral administration (25 or 50 mg) is also effective.*
- *Three to seven days after the methotrexate has been administered, misoprostol (800 microg) is administered by the vaginal route.*
- *Success <56 days: ranges from 84 to 97 percent.*
- *Efficacy*
  - *Immediate success (before misoprostol)*
  - *During the 24 hours after its administration*
  - *Delayed success (>24 hours after misoprotol)*
- *Abortion is often delayed;*
- *12 to 35 percent of women, it occurs approximately 20 to 30 days after the administration of misoprostol*

FUNDAMENTAL QUESTIONS

1. What is the safety of first trimester abortion?
2. What early methods were tried to terminate pregnancies?
3. What is a D&E and a D&C?
4. How are second trimester terminations accomplished today? How about 15 years ago?
5. What is a “saline abortion”?
6. How are prostaglandins employed to terminate pregnancies?
7. What are some of the complications of D&E?
8. What is methotrexate and how does it work?
9. What is the safest method of first trimester abortion?
10. What are some of the theories of the initiation of parturition?
11. Describe the sides effects of prostaglandin therapy for termination.