

Human Reproduction
and
Congenital Heart Disease:
From Biblical/Mythic to
Scientific

ANCIENT GREECE

Pregnancy was regarded as a natural occurrence, not a medical condition. Women in labor were excluded from the sacred sanctuary of Aesclepius because they did not have an ailment that required treatment.



Asexual Human Births

Birth of Eve--From the rib of Adam

Birth of Athena--From the head of
Zeus

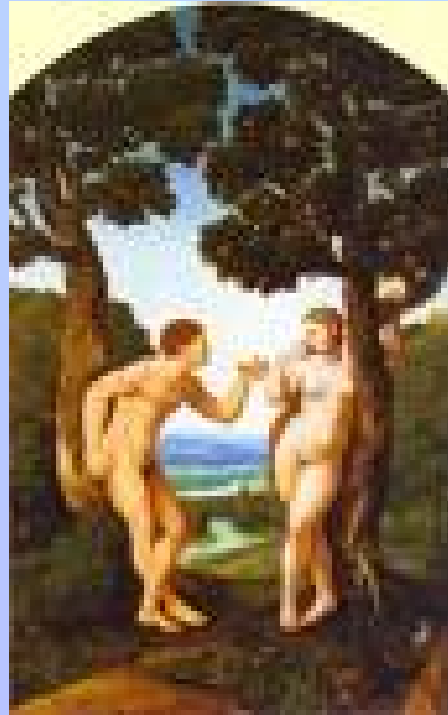
Birth of Aphrodite--From the spume
of the sea

Virgin Births



The Birth of Eve. “And the rib, which the Lord God had taken from man, made he a woman.”

Adam and Eve 16th Century



Before the Renaissance,
theologians taught that Adam
and Eve did not have navels
because they were not born
of woman.



Athena was born of Zeus without a mother. All by himself Zeus fathered grey-eyed Athena. The goddess, fully grown and fully armed, leaped from his head.

Botticelli's Birth of Venus



Round the divine flesh rose up a colorless foam whence grew a maiden
who was called Aphrodite because
she was born from the spume of the sea.

Virgin Births



The earliest account of virgin births was from ancient China circa 600 BC. The offspring were always male. Miraculous birth enhanced the stature of dynastic rulers.



The Pregnant Virgin
Piero della Francesca,
1460

PENGUIN CLASSICS

AESCHYLUS

THE ORESTEIAN
TRILOGY



456 BC

Aeschylus

*The mother is not
the true parent of
the child, but
instead serves as a
passive repository,
a nurse who tends
the growth of the
seed planted by its
true parent-- the
father.*

2006

In vitro Fertilization



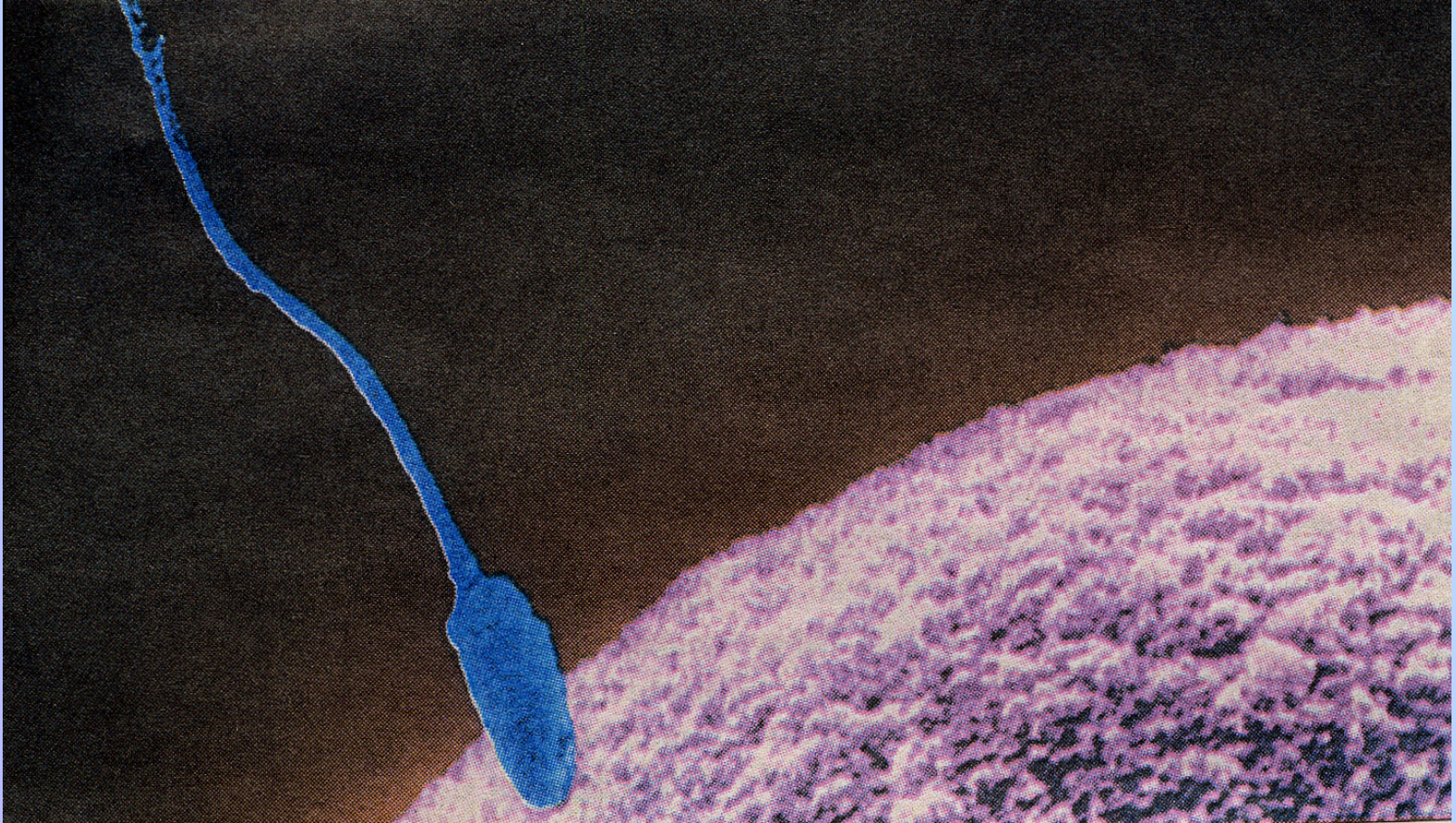
The mother is not the true parent of the child but instead serves as a passive repository, a nurse who tends the growth of the implanted seed--the donor eggs.



Ovaries--*female testes*----were discovered by Herophilus in the 4th century BC. Galen (131 CE) recognized that the female germ originated in the ovaries, and that union with the male sperm takes place in the uterus.

However, for the next 15 centuries, the very discussion of procreation was considered sacrilegious. It is not surprising that the folklore of reproduction was dominated by imagination and fantasy.

Life on the Verge of Beginning

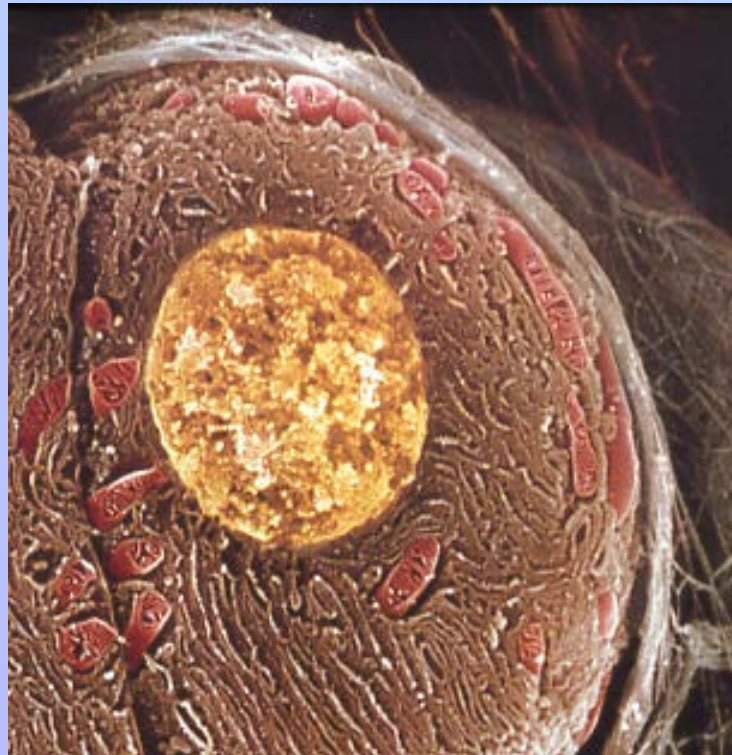


Coloured Scanning Electron Micrograph of a human sperm about to penetrate an egg.

Cell Division That Creates Sperm and Egg

Meiosis, not fertilization, is the crucial event in the reproductive process. Chromosomes replicate, reducing their number by half--from 46 to 23--to form sperm and egg cells. When conception unites the sperm and egg, each contributes 23 chromosomes, resulting in an embryo with a full complement of 46 chromosomes.

How can a tiny speck--the nucleus of the fertilized egg--
contain an elaborate code-script that determines the
entire development of the organism ?



Just as amazing is how often
the tiny speck gets it right !!

Morula

A Four Day Old Embryo



A Pinhead

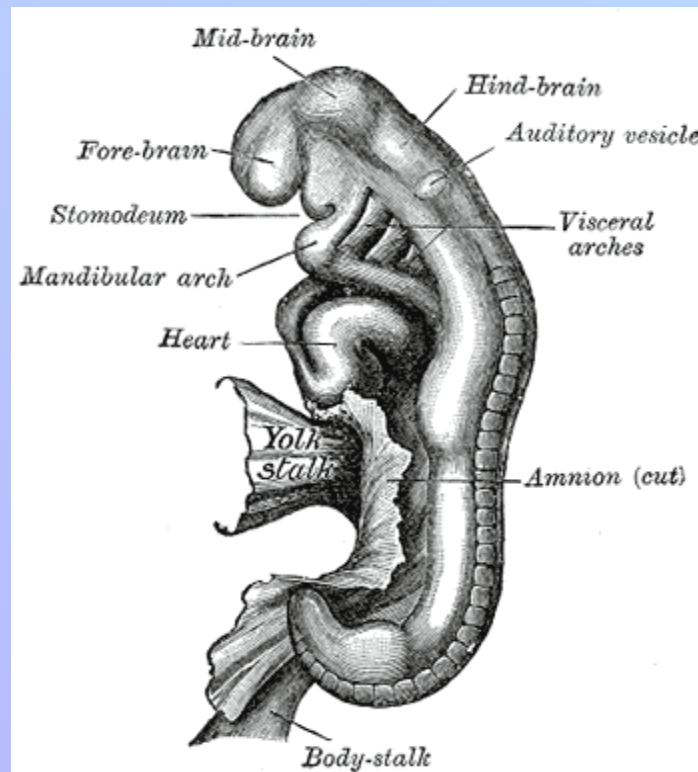




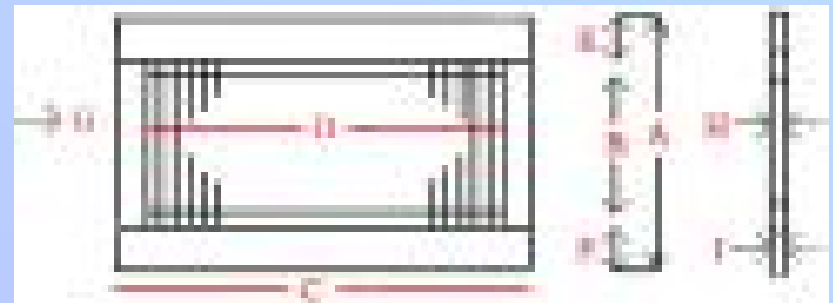
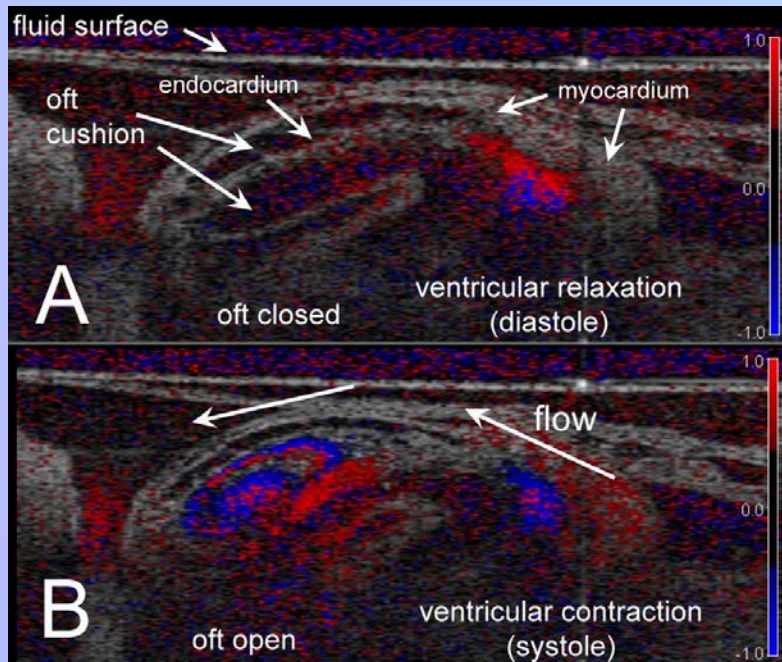
The heart cannot function without beating.

But the heart can beat without functioning.

The fetal heart begins to beat 18 to 21 days after conception. At this stage, the heart serves no circulatory function, but if the beat stops, the fetus dies.



Fluid Dynamics of a 1mm Chick Embryo: Doppler Color Flow



1mm scale

Perinatal Research Institute
Duke University Medical Center
Rothenberg, et al

In the middle ages, fireflies were believed to be the souls of infants who who died before baptism.





The Church used enemas filled with holy water to perform intrauterine baptism when the life of the unborn infant was threatened.

William Hunter

The Human Gravid Uterus

1774



Leonardo da Vinci

Fetus Within the Womb

1510

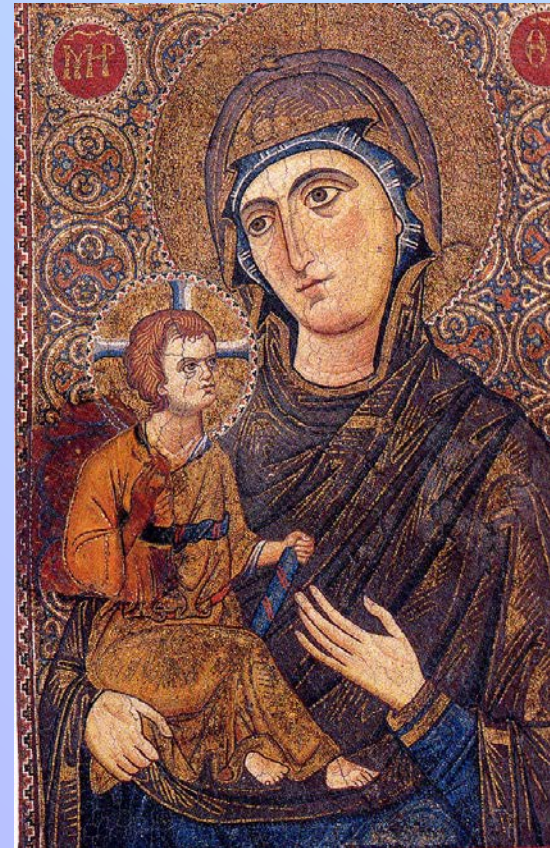


The Homunculus Preceded Developmental Biology

At the moment of conception,
there is a fully-formed human
being --an *homunculus*--that
doesn't develop, but merely
increases in size during gestation.

13th Century

The infant is not an infant, but
a small adult--an homunculus



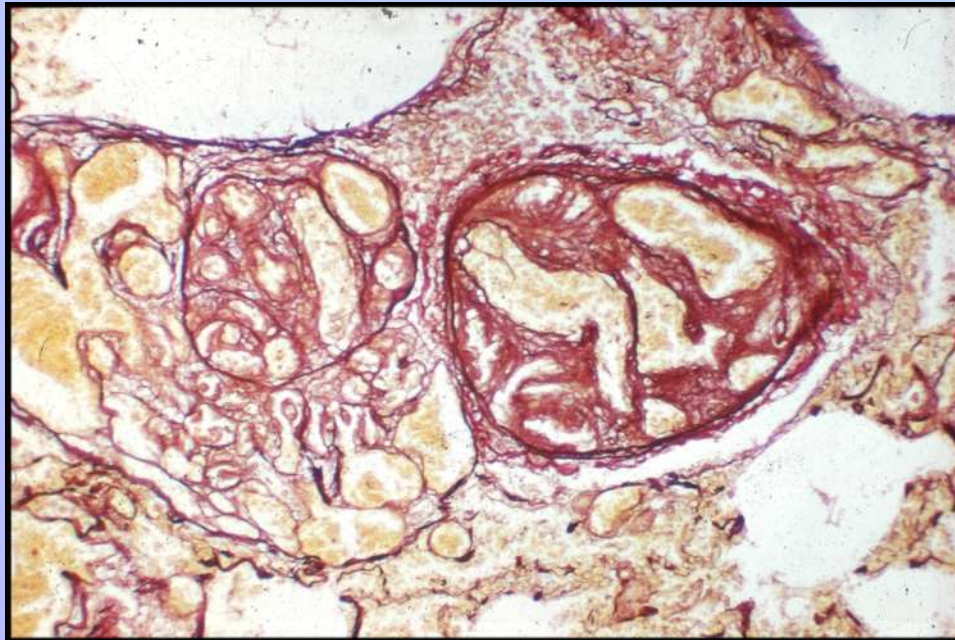
Human Reproduction and Congenital Heart Disease

A complex interplay between maternal
circulatory and respiratory physiology,
and maternal congenital heart disease,
and the effects of this interplay on the
fetus

Major Maternal Risks

Why The Mother Dies

- Pulmonary vascular disease
- Pulmonary edema



Maternal mortality with pulmonary vascular disease reaches 50%.

Major Fetal Risks

Why the Fetus Dies

Maternal Death

Maternal Functional Class

Maternal Cyanosis

Oral Anticoagulants

Maternal Mortality According to Functional Class

Classes I and II

0.4%

Classes III and IV

6.8%

Fetal Mortality According to Maternal Functional Class

Class I

nil

Class IV

30%

Cyanosis

Intrauterine Hypoxemia

Dysmaturity and fetal wastage



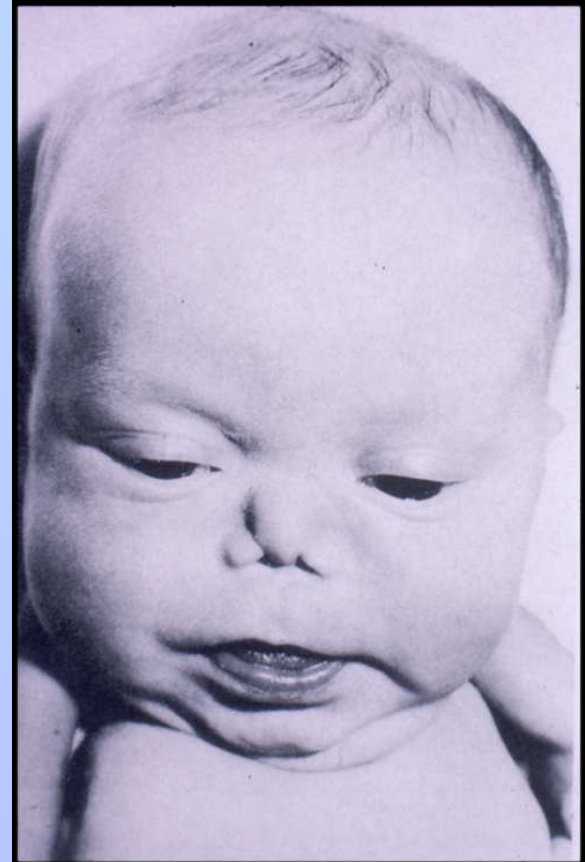
Anticoagulation in Pregnant Women with Mechanical Heart Valves

No anticoagulant regimen provides
maximum protection at no risk.



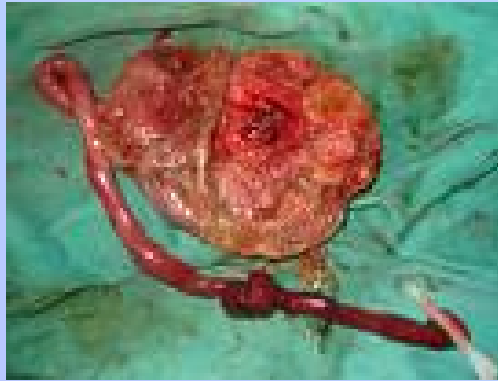
Warfarin Embryopathy

- Facial dysmorphism
- Growth Retardation
- Microcephaly
- Mental retardation:
*the brain does not
obey the rules of
organogenesis*



Coumadin

Preterm Labor and Hemorrhagic Fetal Death

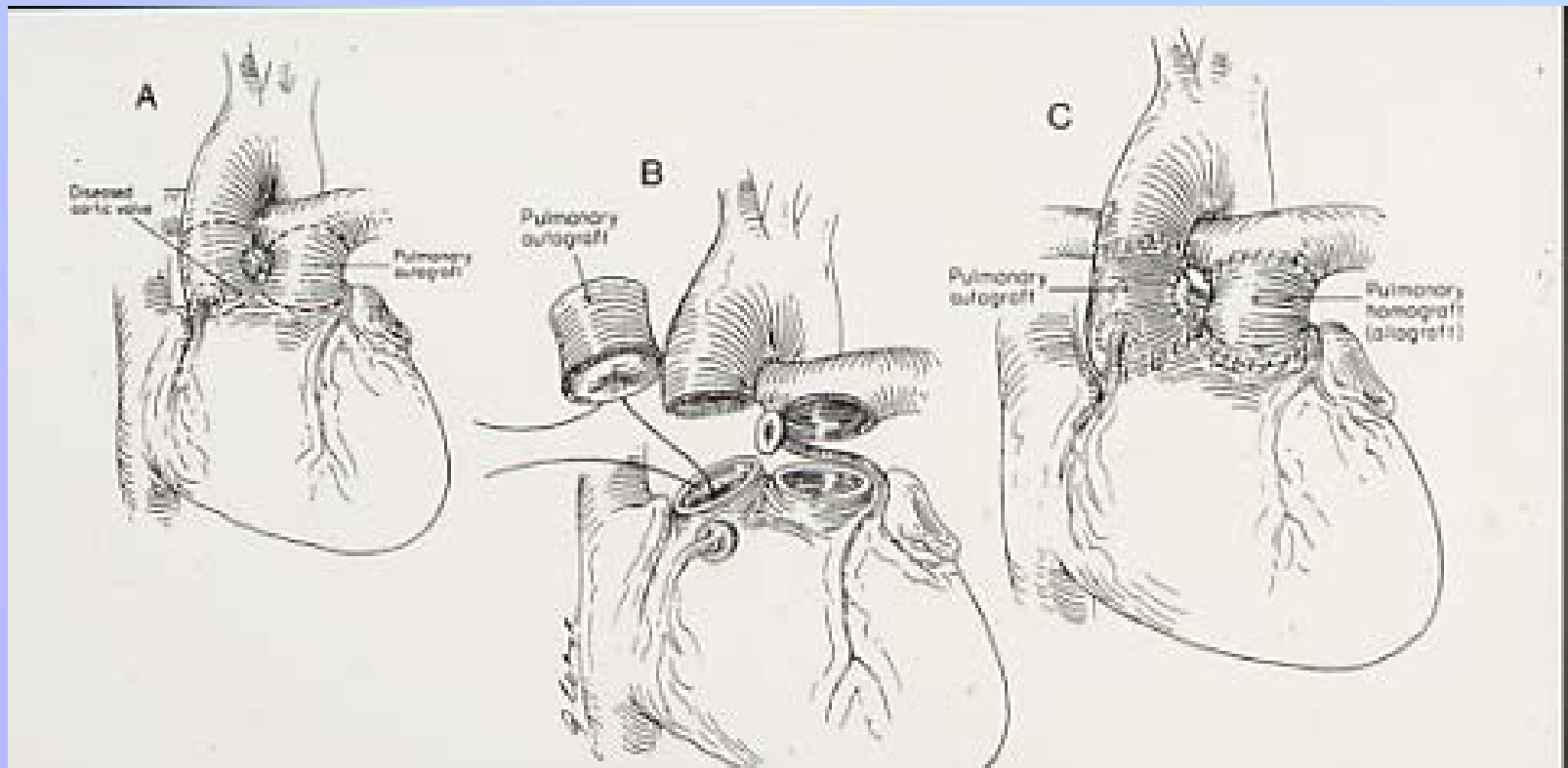


Fetal anticoagulation cannot be reversed.

Cesarean delivery reduces the risk of hemorrhagic fetal death.

The Ross Procedure

Anticoagulants are not Needed

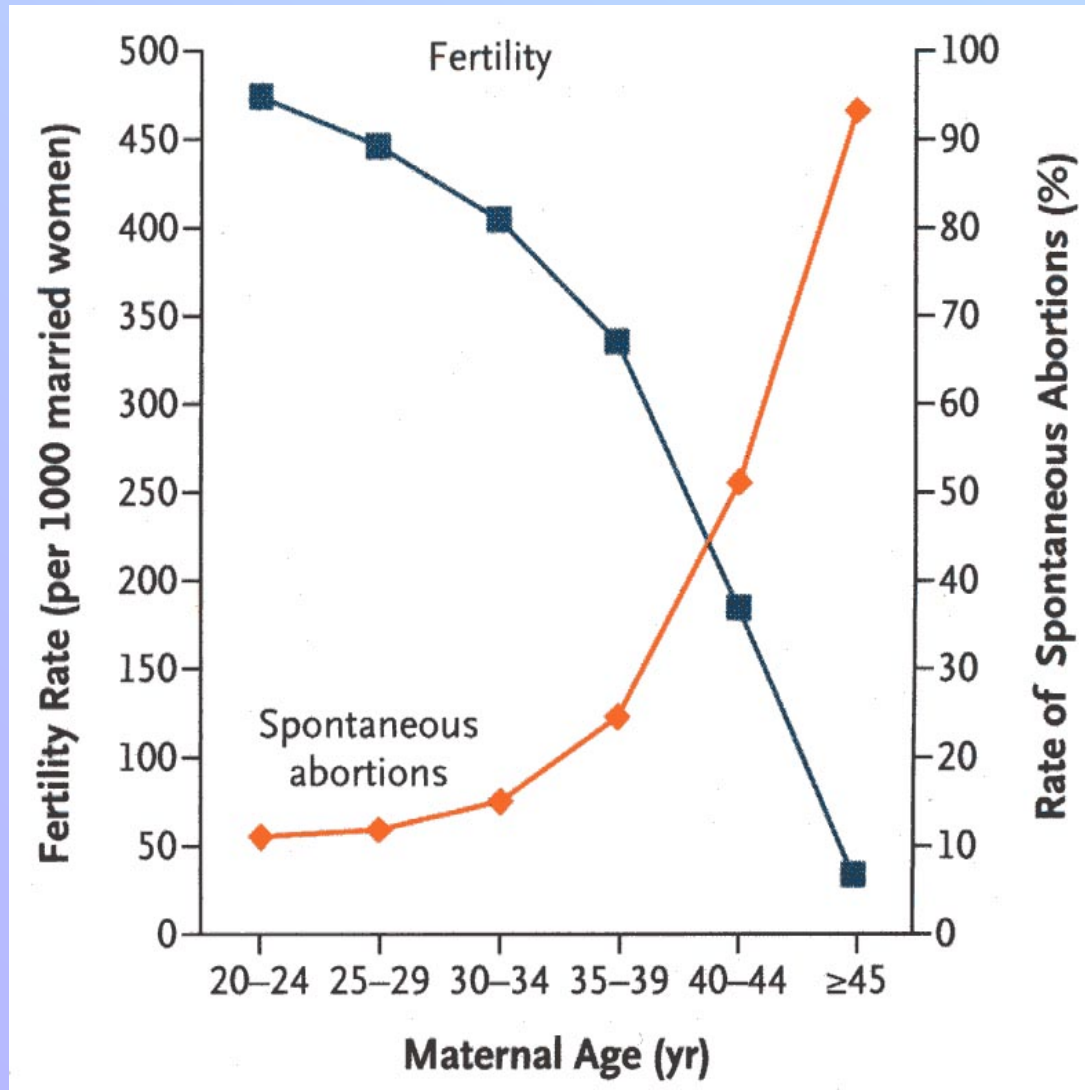


Maternal Age

Risk of Down's Syndrome and Chromosomal Abnormalities at Live Birth, According to Maternal Age.*

Maternal Age at Delivery (yr)	Risk of Down's Syndrome	Risk of Any Chromosomal Abnormality
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21

Fertility and Miscarriage as a Function of Maternal Age



Hemodynamic Effects of Major Uterine Contractions

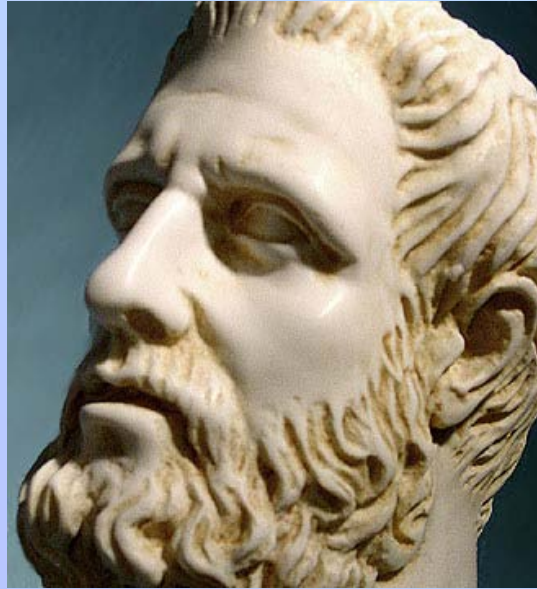
1. 25% increase in cardiac output
2. 35% increase in stroke volume
3. 10% increase in systemic blood pressure
4. 300-500 cc of blood is expressed into the proximal systemic vascular bed
5. The effect of maternal position
6. The effects of pain-- “Eve He punished by childbirth and its attendant pain because she had deluded Adam.”

*A Remarkable Account of the
Pain of “Natural” Childbirth*

“Suddenly there was a scream unlike
anything he had ever heard”

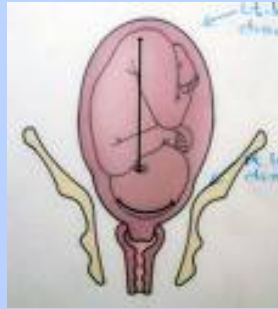


Kitty's Labor
in
Tolstoy's
Anna Karenina



Hippocrates believed that the foetus had to fight its way out of the womb, breaking the membranes in its struggle.

Cesarean, caedere (L) to cut



The history of “cesarean” remains shrouded in mystery. In many early societies, the body of a dead pregnant woman could not be buried before her child was removed. Until the 16th century, cesarean delivery was reserved for the tragic event of maternal death during labor.

“Cesarean” did not refer to the birth of Caesar, but Roman law decreed that a woman who died in labor must undergo post-mortem delivery. The Catholic Church established a similar decree in order to baptize the baby.



Apollo snatched his mortal son Aesclepius, from
the womb of Coronis, the dead mother



Pierre Boaistuau 1560

Here recounts the gruesome birth of a woman who for an incredible 5 years carried her dead child within the womb. She pleaded to be opened and for the dead baby removed. The operation was successful. The woman survived and bore additional children.

Cesarean Delivery

DISADVANTAGES

- Blood loss is over twice as great as with vaginal delivery
- Blood loss is even greater in cyanotic gravida
- Complications accompany delayed ambulation
- Anesthetic hypotension increases right-to-left shunts and maternal hypoxemia

Cesarean Delivery

Obstetrical Indications

Cephalopelvic disproportion

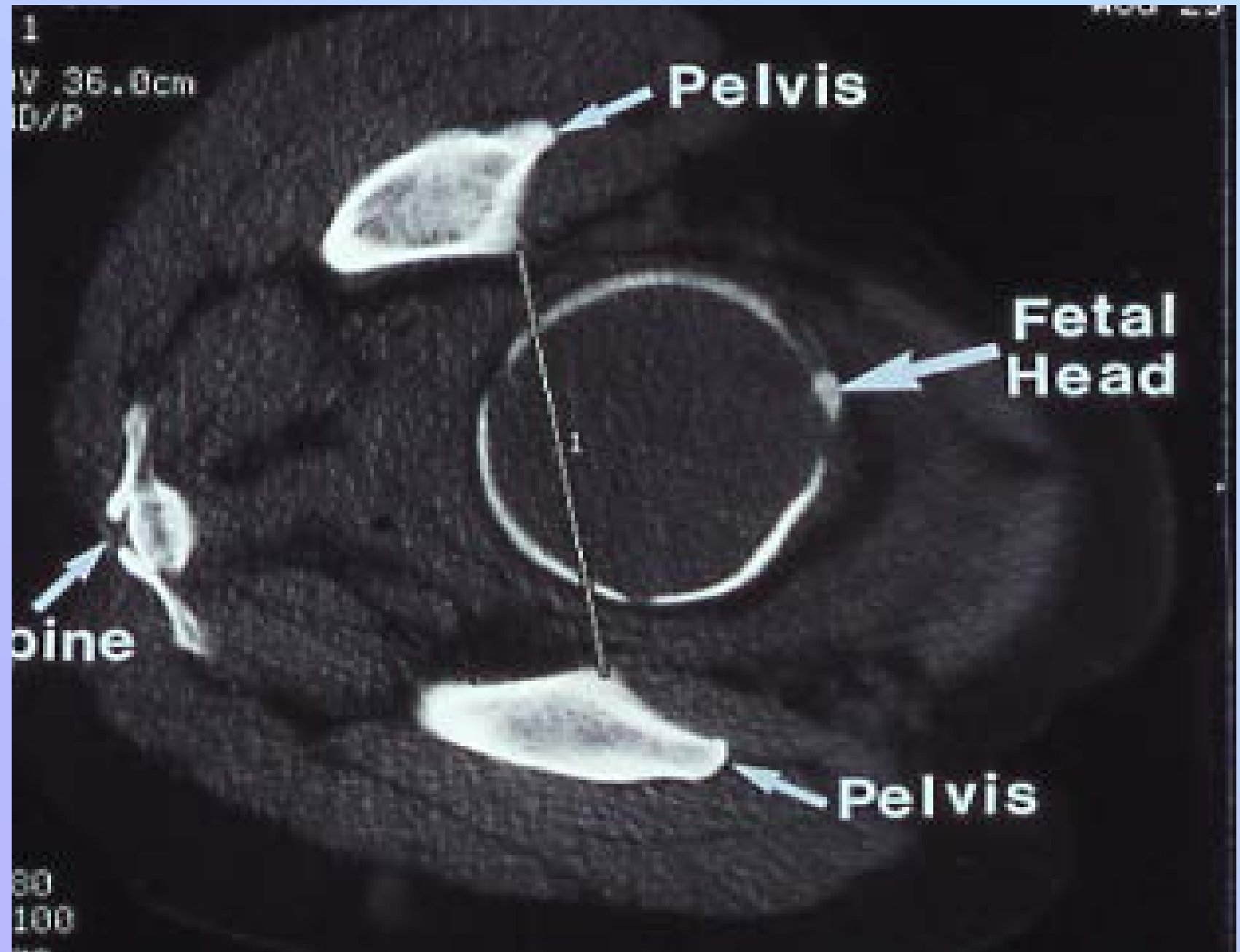
Breech presentation

Placenta praevia

Preterm labor in an anticoagulated gravida

Preeclampsia

Cephalopelvic Disproportion--No Need to Guess



A Tragic Breech



The Pennsylvania Hospital Historical Collections

16th Century



Paracelsus believed that fate was determined by the stars
overhead at the time birth.

Sixteenth Century German Engraving



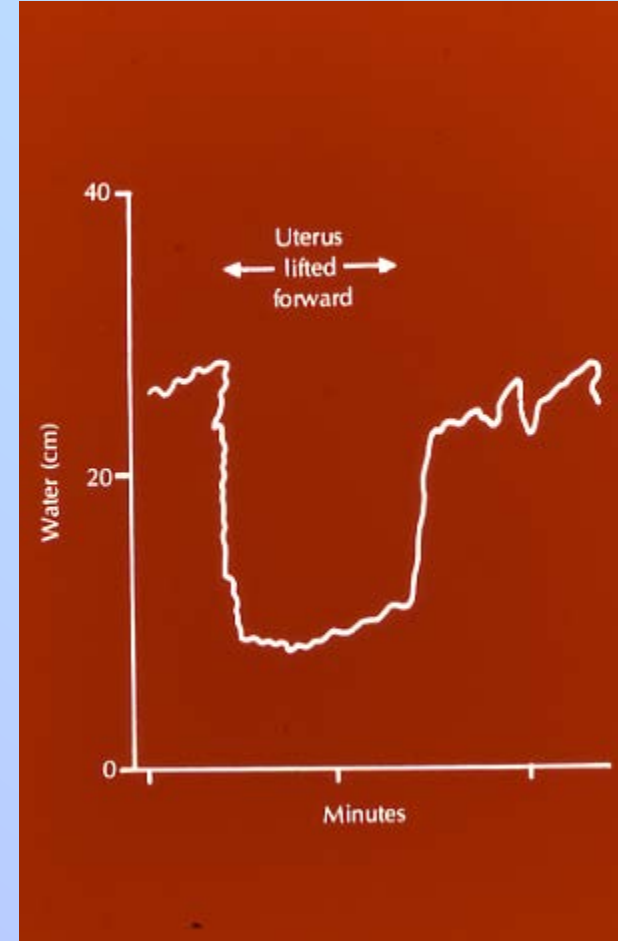
The gravida squatted over a bed of clean straw with her heels on *birthing bricks*,. The bricks used in ancient Egypt were 14 by 7 inches long and were decorated with colorful painted scenes and figures of the birth process.

Maternal Position According to Scripture

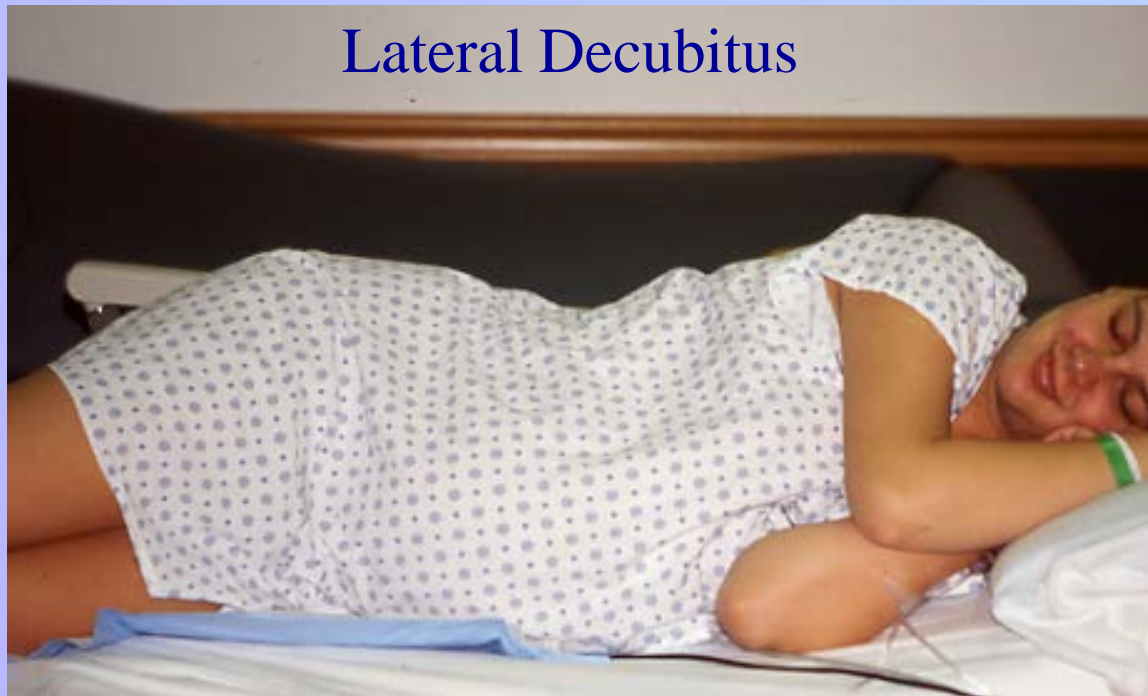
The Second Book of Moses called **EXODUS**

And he said, “When ye do
the office of a midwife to
the Hebrew women, see
them upon the stools.”





Lateral Decubitus



21st Century
Maternal
Position

Etherization in Childbirth

“Unto the woman he said...In sorrow thou shalt bring forth children.”



In 1846, Crawford Long in the United States discovered that surgical operations could be performed without suffering by inhaling the vapor of sulfuric ether. It was soon realized that labor could also be accomplished without pain by use of the same vapor.

Elective Controlled Vaginal Delivery

Current Practice

Amniocentesis in the 37th week to determine fetal lung maturity

Intravaginal and intracervical prostaglandins to soften and dilate the cervix

Relief of pain and apprehension—meperidine and lumbar epidural anesthesia

Uterine contractions unassisted by bearing down

Pain-free labor in a lateral decubitus position

Vacuum extraction with low forceps

Infective Endocarditis



Bacteremia is not a necessary accompaniment of normal uncomplicated vaginal delivery. But can “normal” and “uncomplicated be predicted?

Prophylaxis – Ampicillin/Gentamicin,
Vancomycin

Common Malformations with Expected Adult Survival

Approximate Order of Female Prevalence

ACYANOTIC

Atrial septal defect (secundum)

Patent ductus arteriosus

Pulmonary valve stenosis

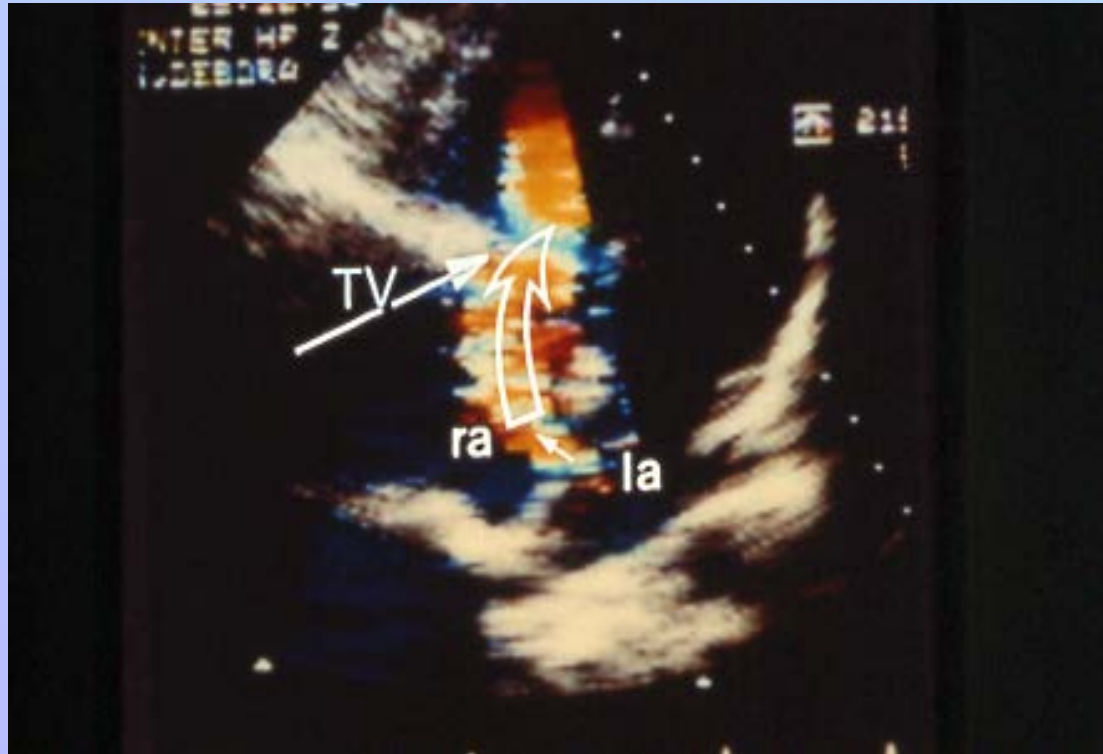
Coarctation of the aorta

Bicuspid aortic valve

CYANOTIC

Fallot's tetralogy

Pregnancy in Secundum ASD



Acute blood loss decreases systemic venous return and increases the left-to-right shunt

Thromboembolism

IVC compression increases lower extremity venous pressure, and progesterone attenuates peripheral veins, predisposing to thrombus formation.

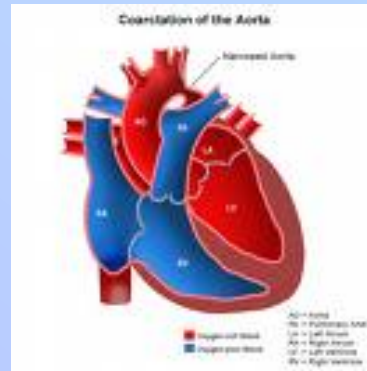
Changes in maternal coagulation and fibrinolytic systems adversely alter hemostasis.

The interatrial communication sets the stage for a paradoxical embolus.

Moderately restrictive calcified PDA
Female age 57 years, 20 pregnancies



COARCTATION of the AORTA



Major Complications

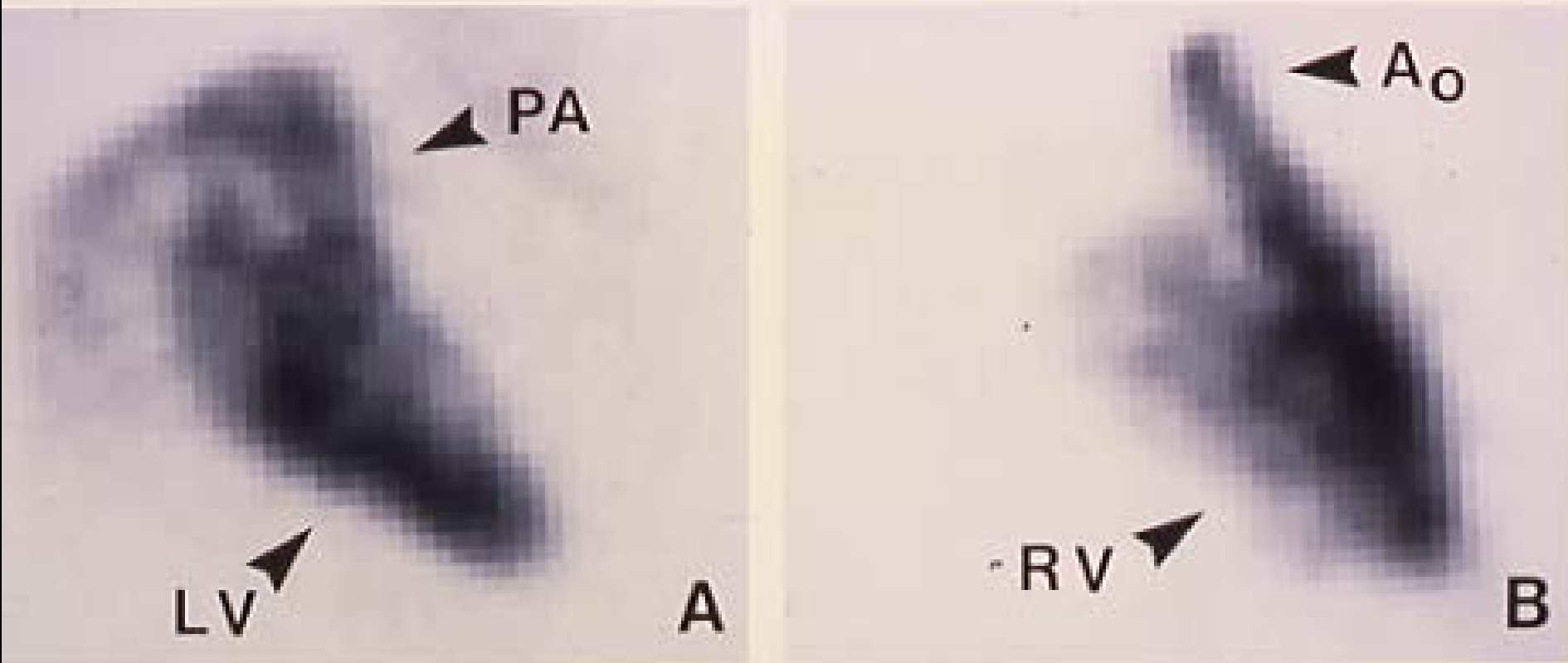
Left ventricular failure

Infective endocarditis or
endarteritis

Rupture or dissection of the
vulnerable para-coarctation aorta

Cerebral hemorrhage

Congenitally Corrected Transposition



Failure of the subaortic morphologic right ventricle
High Degree Heart Block

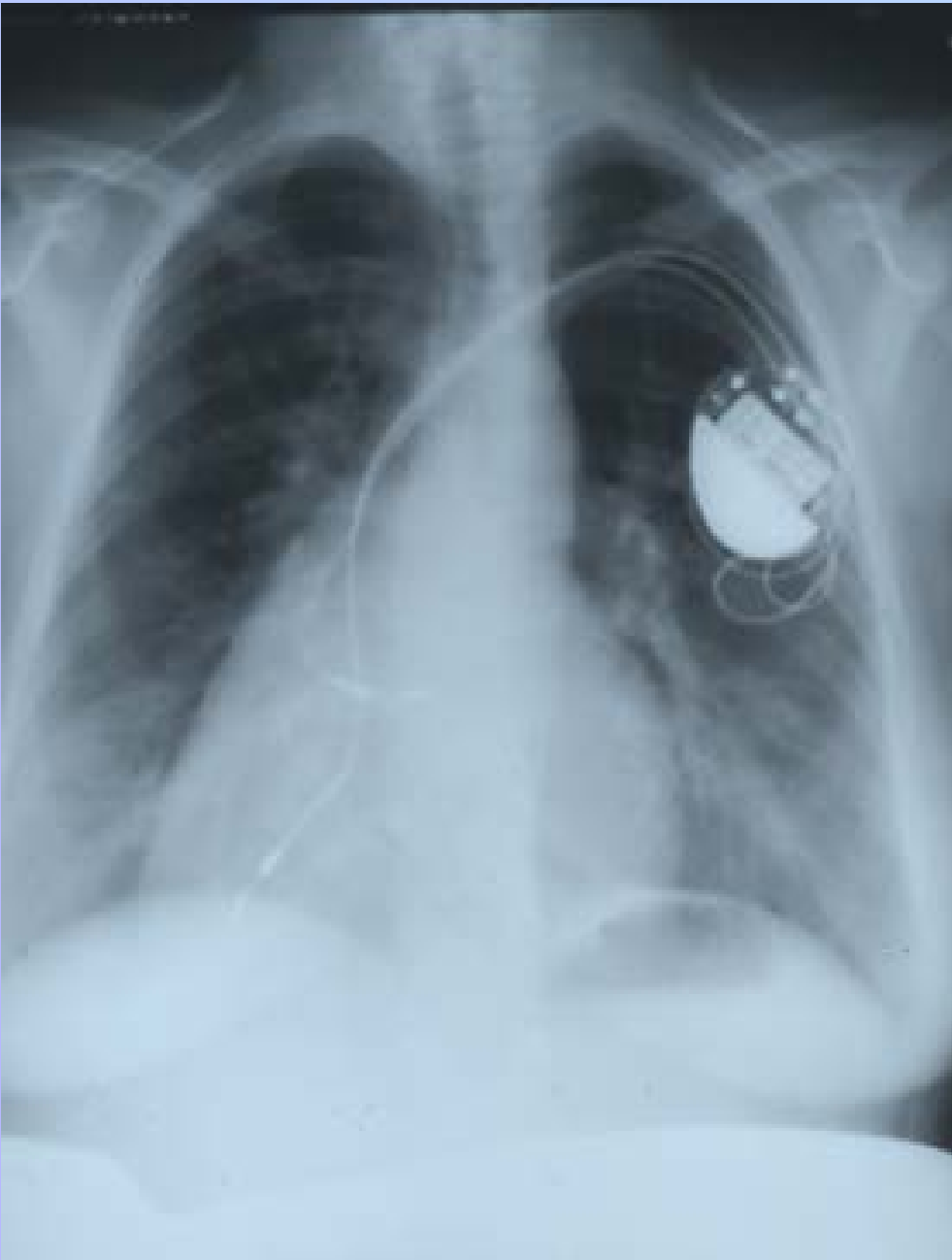
Congenitally Corrected Transposition

Five pregnancies.

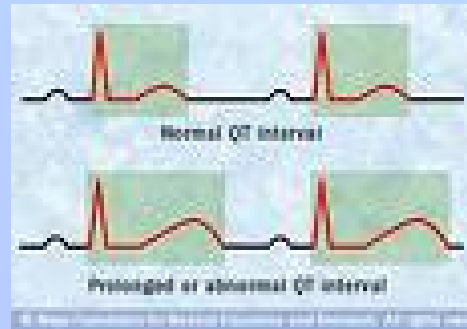
Which is the 52 year old mother ?



Happy Ending



Pregnancy and the Long QT Syndrome



Syncope, aborted cardiac arrest & death
during three 40-week periods

- 1) Pre-conception – nil
- 2) During pregnancy – nil
- 3) Postpartum – increased prevalence

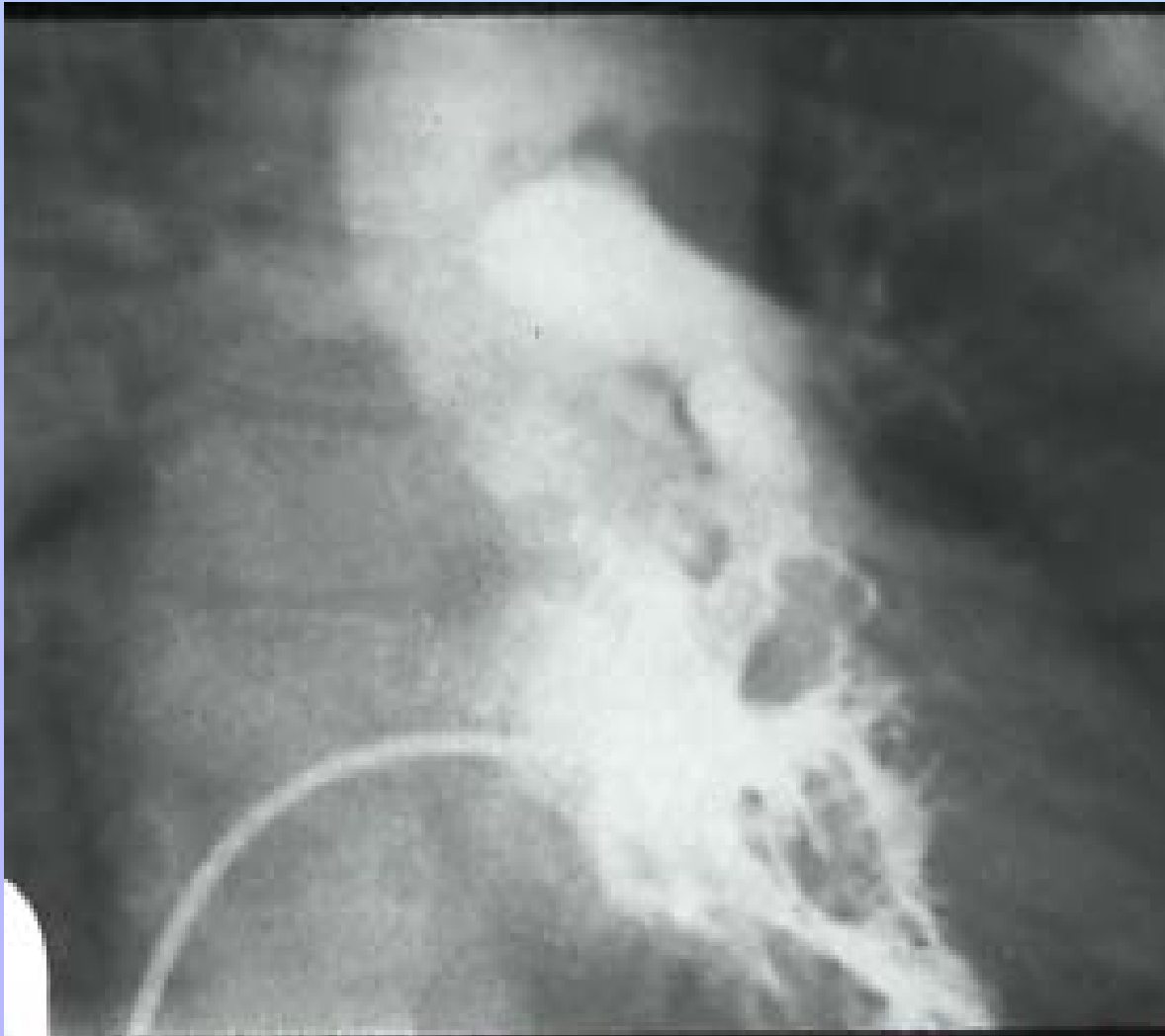
Postpartum is associated with a significant increase in prevalence of cardiac events among probands with the long QT syndrome.

Triggers: Adrenergic or auditory stimuli.

Beta-adrenergic blockade during gestation should be continued postpartum.

Pregnancy in Cyanotic Congenital Heart Disease

Tetralogy of Fallot



Fallot's Tetralogy

- 1) *Gestational fall in SVR* provokes increased R-to- L shunt, hypoxemia, dysmaturity, fetal wastage.
- 2) *Labor, delivery, puerperium:*
 - a) A sudden *rise* in SVR (bearing down) abruptly and dangerously reduces systemic and cerebral blood flow.
 - b) A sudden *fall* in SVR precipitates intense cyanosis, syncope and death.

Eisenmenger Syndrome and Pregnancy

A Catastrophe Waiting to Happen

1. Gestational *fall* in SVR increases R-to L shunt
2. *Labor, delivery, puerperium:*
 - a) Sudden *rise* in SVR (bearing down) abruptly and dangerously reduces systemic and cerebral blood flow.
 - b) Sudden *fall* in SVR precipitates intense cyanosis, syncope and death.

Eisenmenger Syndrome



Risks of a flotation catheter outweigh benefits. An arterial line and a pulse oximeter suffice.

Efficacy of oxygen during labor is doubtful but unproven.

Red Cells, Plasma Volume & Hemostasis During Gestation

1. First and Second Trimesters:

- a. Plasma volume increases in excess of red cell mass
- b. Hematocrit and hemoglobin fall
- c. Red cells become thicker and more spherical because of remodeling in the placenta

2. Third Trimester and Term:

Hormone-induced hypercoagulability

Labor

Hypercoagulable state due to enhanced platelet activation and elevated fibrinogen and Factor VII

Placental Separation

Hypercoagulable state persists, but enhanced fibrinolysis assists in clearing fibrin residue.

Postpartum

Persistence of a hypercoagulable state and enhanced fibrinolysis for 24 hours.

Caveats Regarding Heparin in Cyanotic Congenital Heart Disease

Risks Outweigh Benefits

1. Heparin is an antiplatelet agent
2. Platelet counts are low-normal or thrombocytopenic in CCHD
3. Hypercoagulability doesn't occur in the first or second trimester, and is variable during the third trimester

Caveats, contd.

4. There are no reliable tests for measuring generation of thrombin and levels of antithrombin
5. Commercial APTT agents differ in their responses to heparin
6. Heparin pharmacokinetics are complex, and the hemostatic substrates in gravidas with CCHD are variable

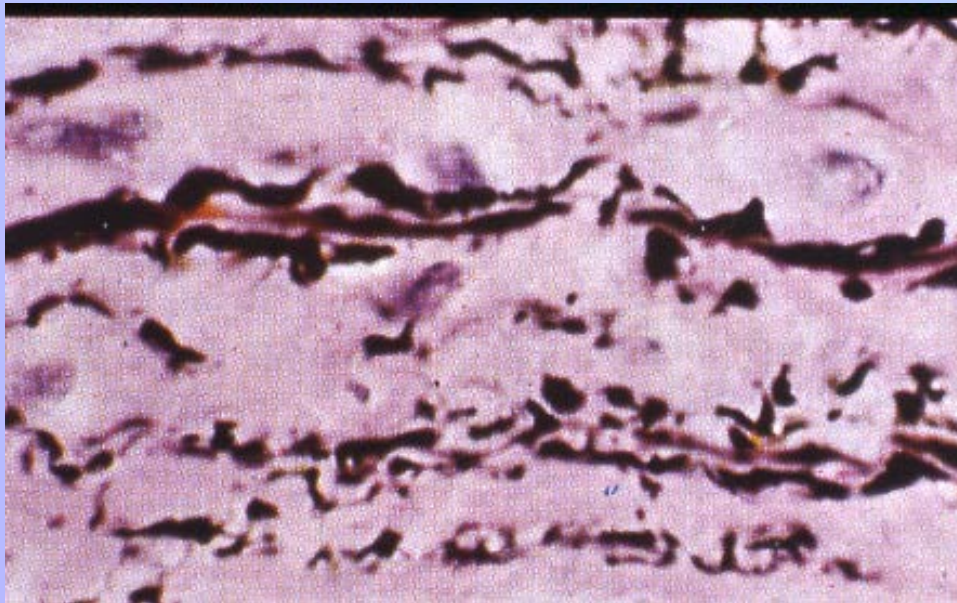
Congenital Cardiac Patients of Childbearing Age: An Increasing Population

Pre-gestational surgery and interventional catheterization improve the health of mother and child, and the safety and success of pregnancy.

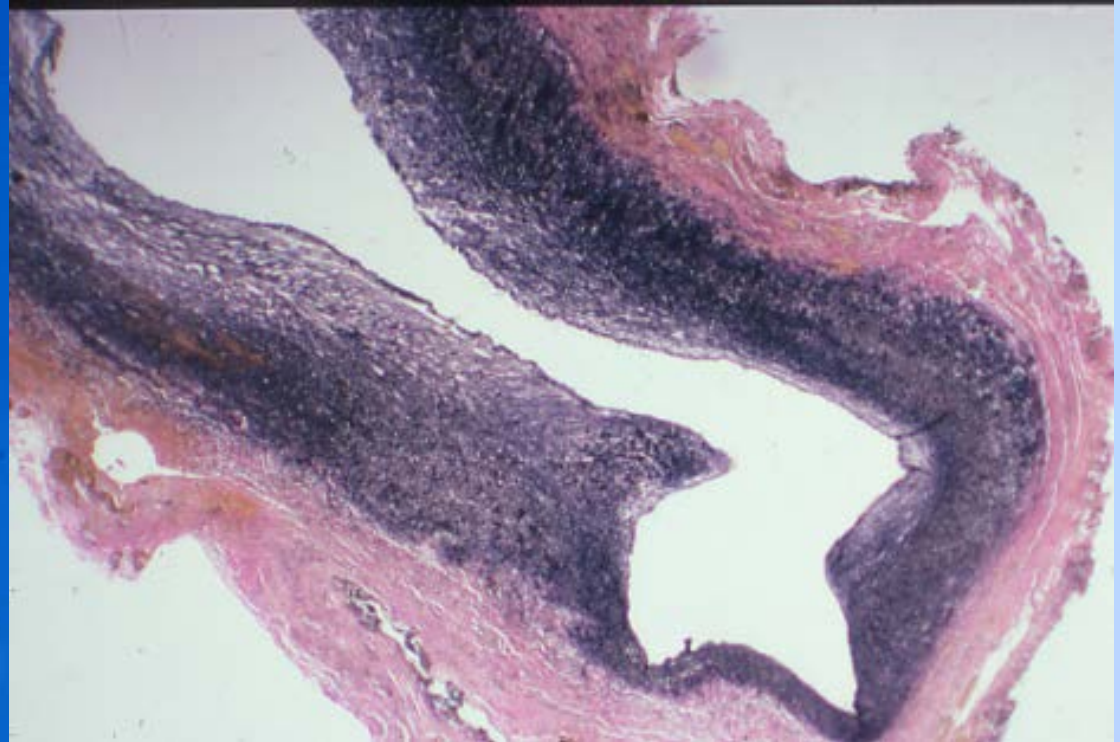
Non-gravid aortic media



Gravid aortic media



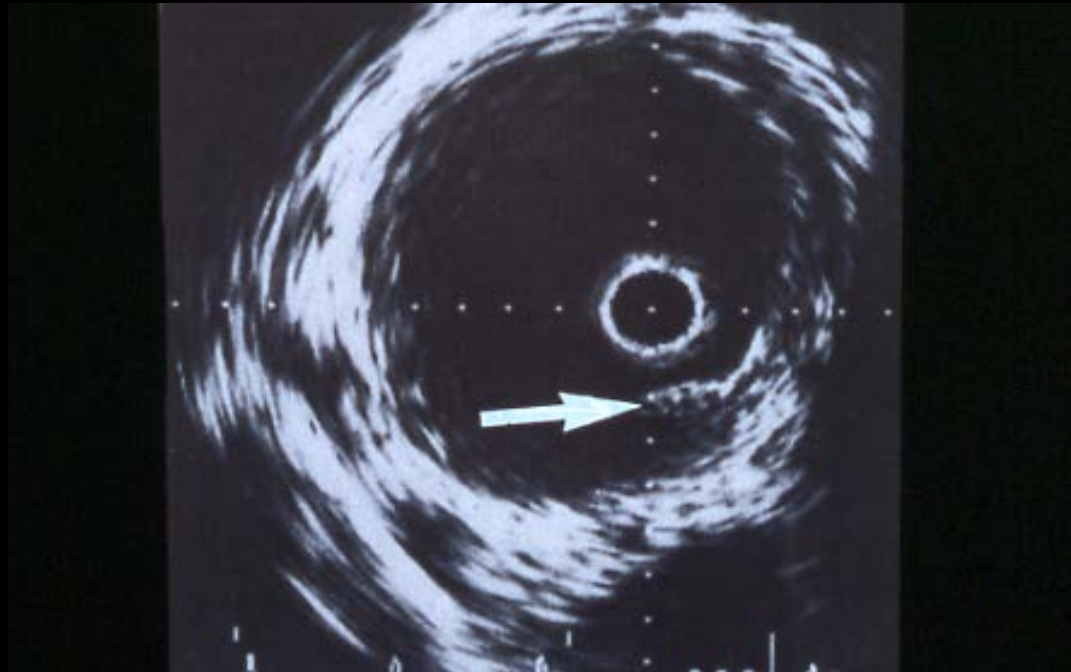
Coarctation



The Vulnerable
Paracoarctation Aorta

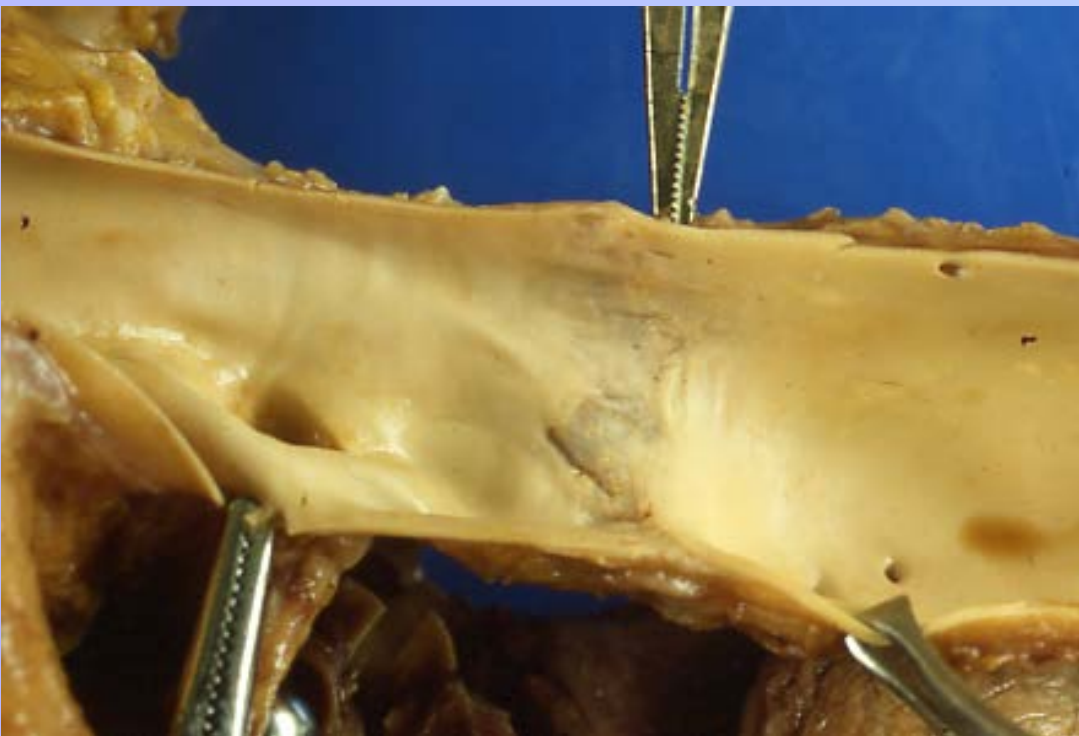
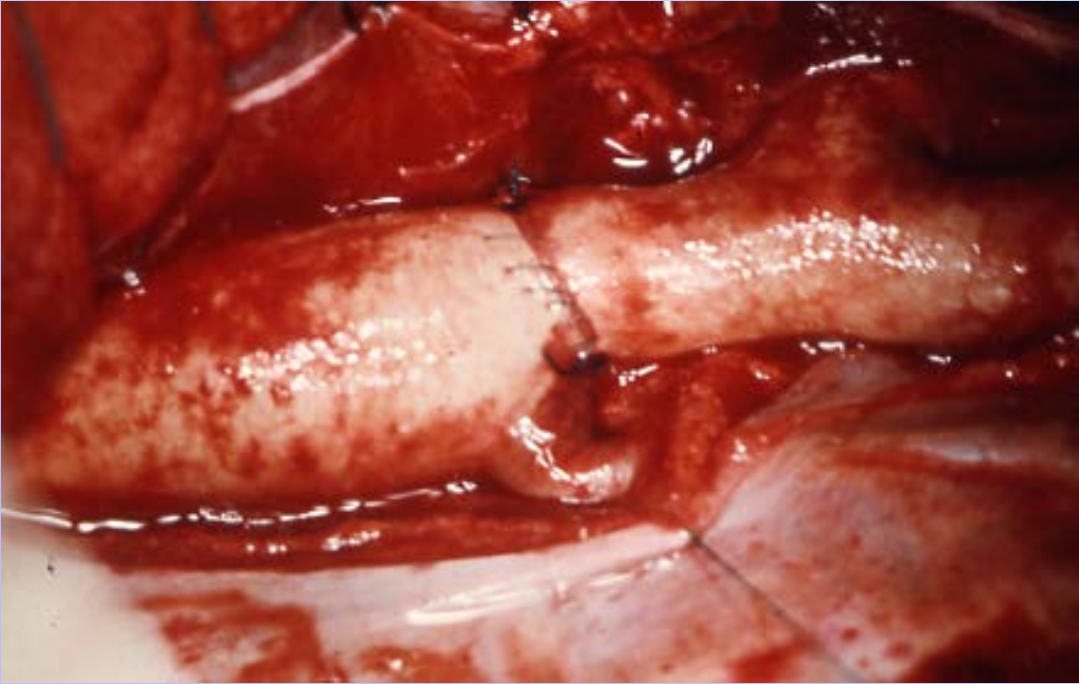


Balloon Dilatation of Coarctation



Intravascular Ultrasound

Anatomic Success

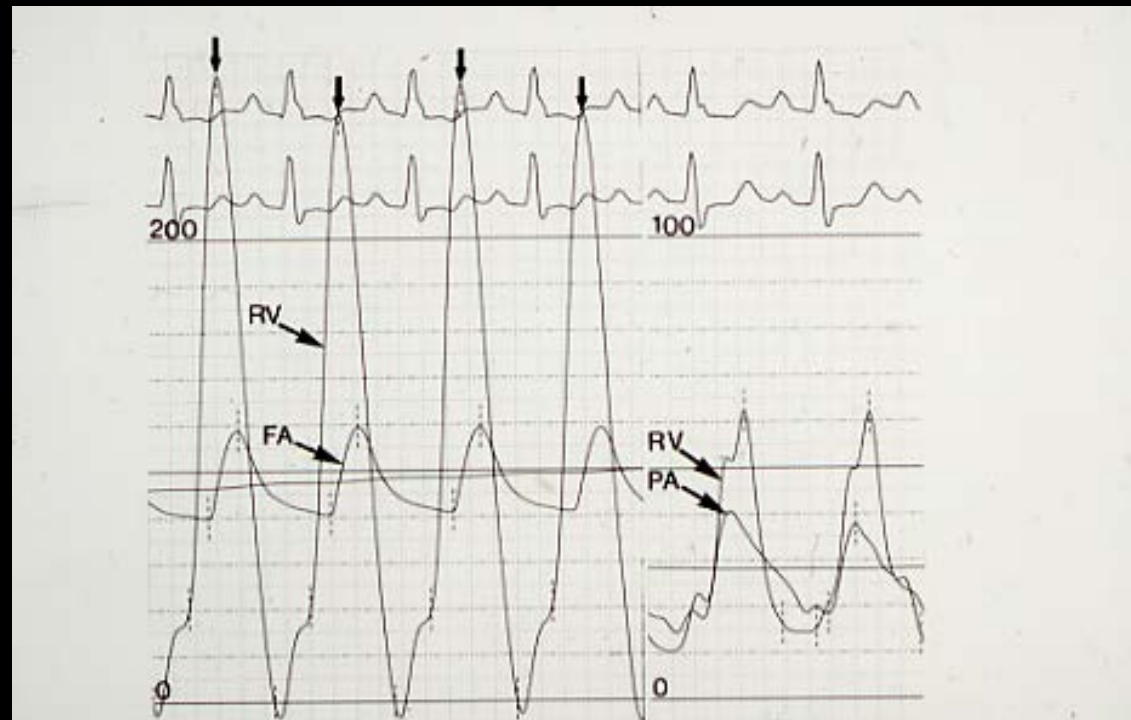
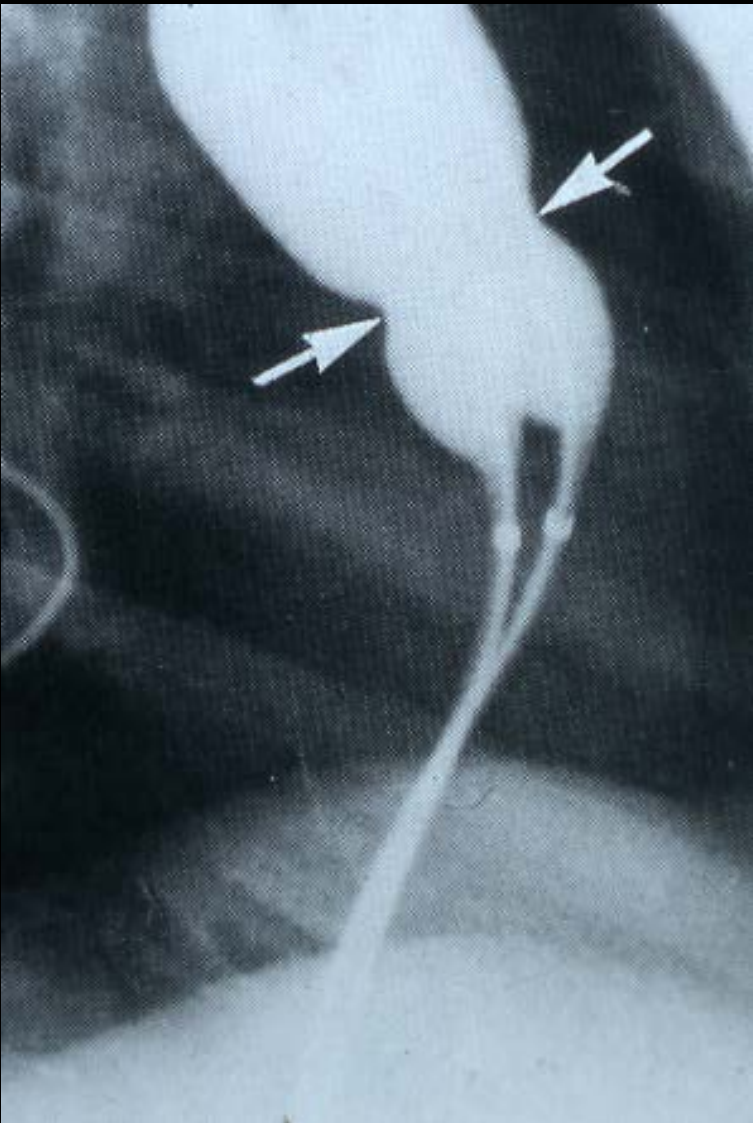


Gadolinium

Severe Pulmonary Valve Stenosis Third Trimester Balloon Dilatation

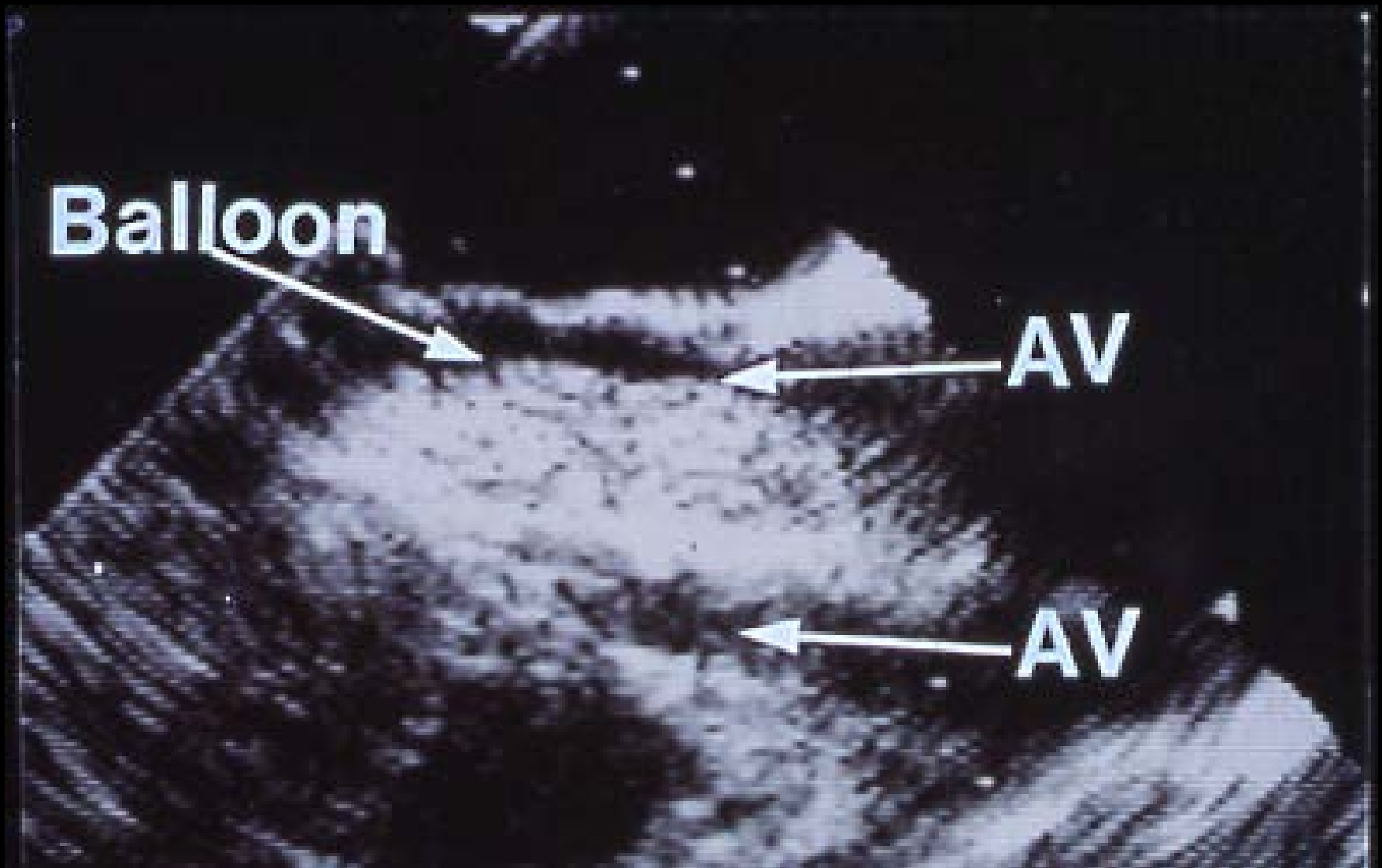


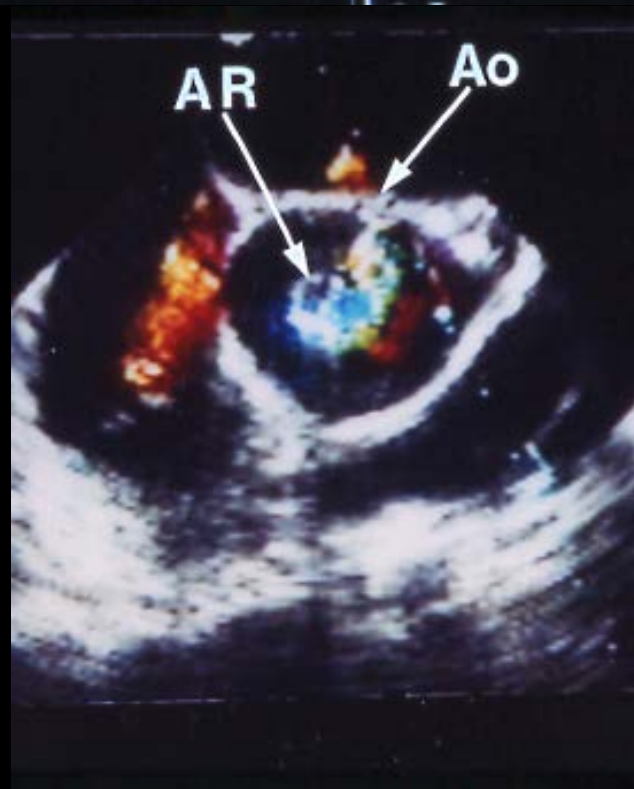
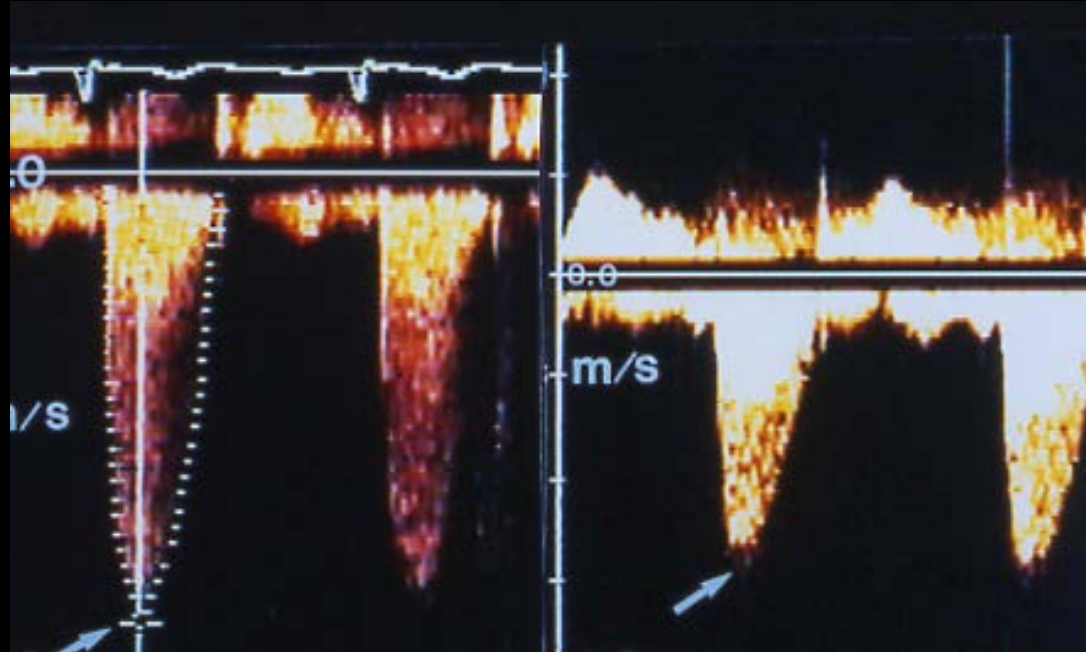
Pulmonary Valve Stenosis



Balloon Valvotomy

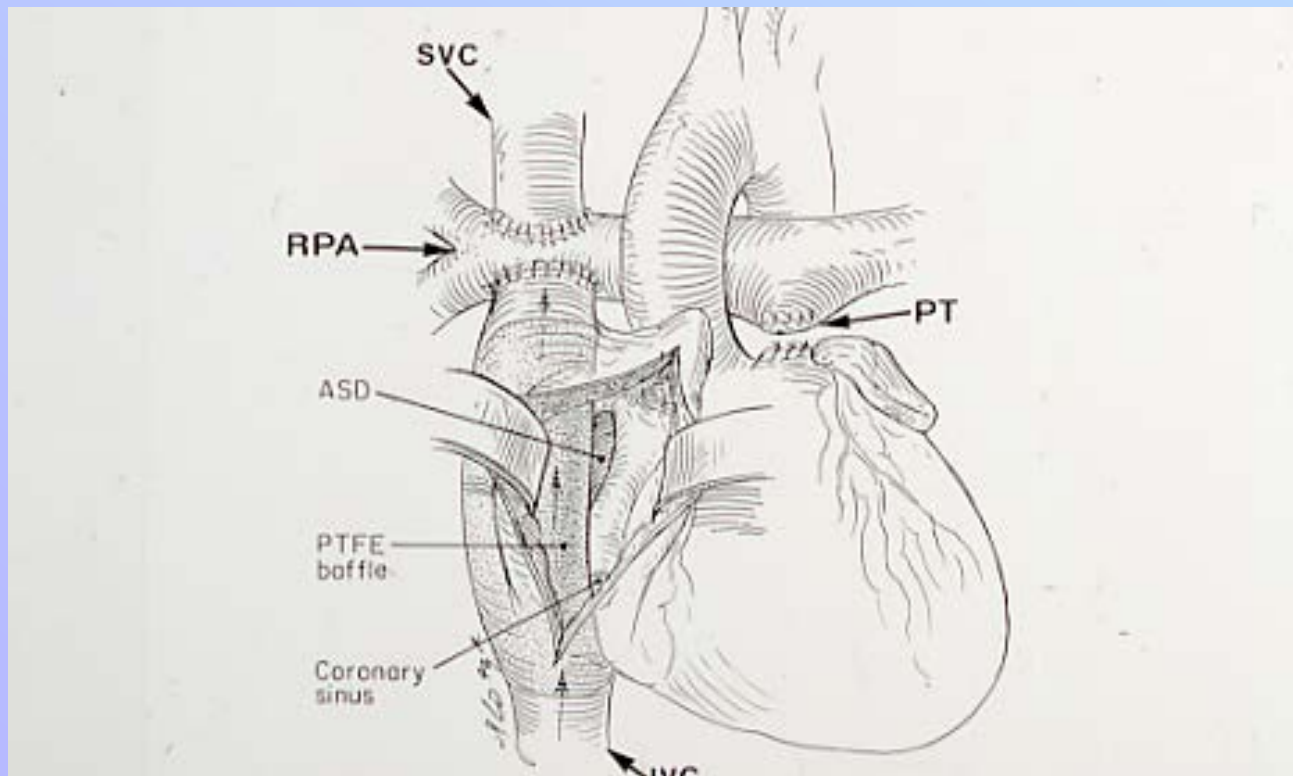
Severe Bicuspid Aortic Stenosis Third Trimester Balloon Dilatation





Pregnancy after Repair of Complex Cyanotic Congenital Heart Disease

Fontan repair for single ventricle or tricuspid atresia



Ventricular function/atrial tachyarrhythmias

*Complete Transposition
of the Great Arteries:*

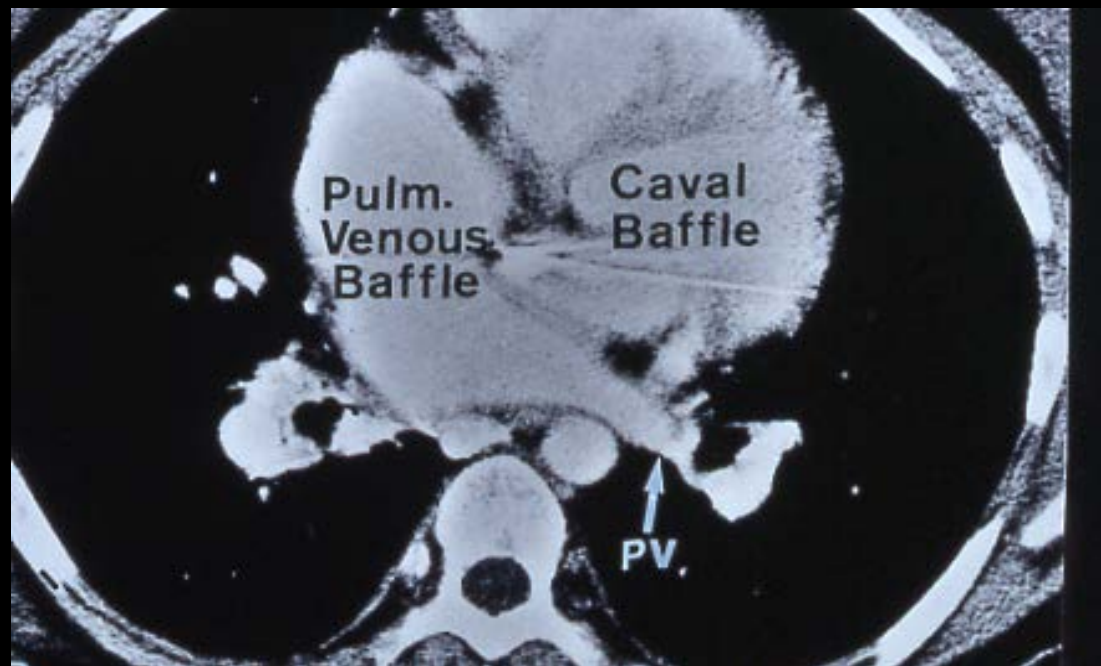
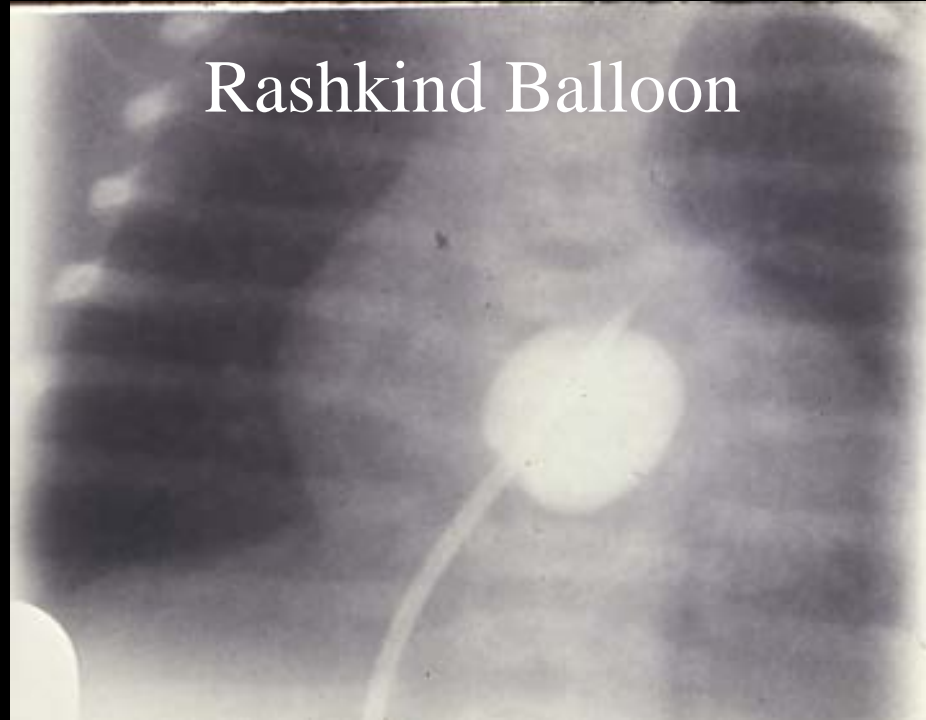
Death rate without intervention

30% in the first week

50% in the first month

90% in the first year

Rashkind Balloon





Complete Transposition

Atrial Switch



Survival Patterns in Fallot's Tetralogy

1 st birthday	---	66%
Age 3 years	---	50%
Age 10	---	25%
Age 20	---	11%
Age 30	---	6%
Age 40	---	3%

Paternal Fallot's tetralogy, operation and reoperation. Normal offspring



Remote Risks To The Fetus

Parental transmission

**Teratogens, environmental toxins and
environmental exposures**

Congenital Heart Disease

Fetal Recurrence

Incidence in the General Population	0.4% to 0.6%
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One affected sibling	2.3% (1.5 to 3X)
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Two affected siblings	7.3% (5 to 10X)
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Affected mother	6.7% (2.5 to 18X)
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Affected father	2.1% (1.5 to 3X)
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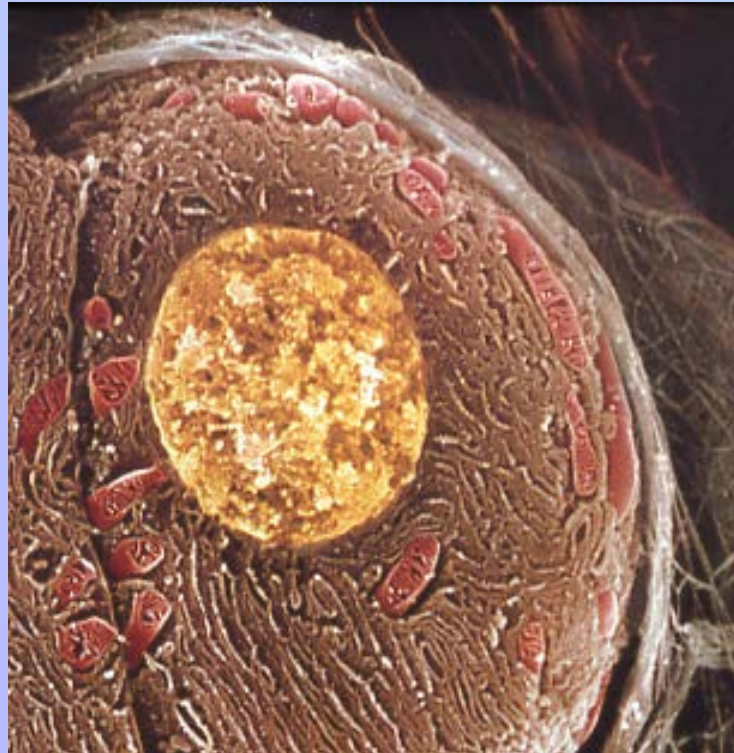
Maternal Transmission

Cytoplasmic Inheritance

Parental Imprinting

Maternal Inheritance of Mitochondria

A distinguishing feature of cytoplasmic material such as mitochondria is a tendency for inheritance through the female line.



Paternal Imprinting

Non-Mendelian behavior of certain autosomal genes, the expression of which depends upon the sex of the parent from which the gene is inherited.

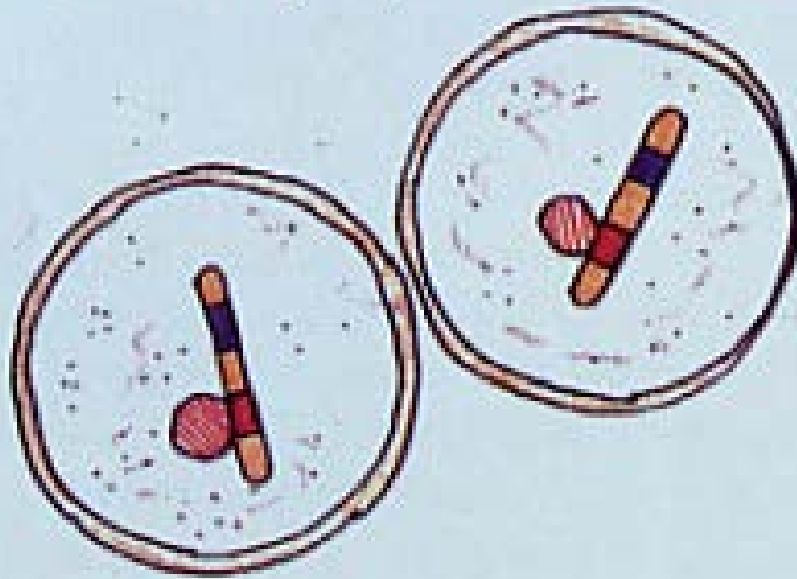
The pattern of transgene expression correlates with the state of parentally imprinted methylation.

Parental Imprinting

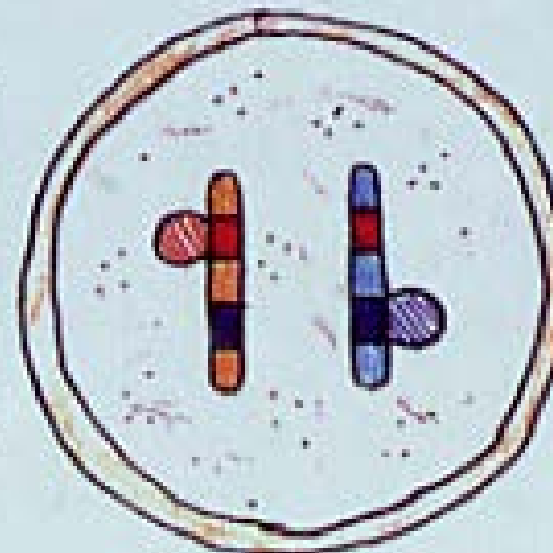
DNA Methylation and Gene Expression

maternally imprinted chromosomes

paternally imprinted chromosomes



MIB		OIF			maternal chromosome
PIB		SIF			paternal chromosome
					amnesic chromosome



Embryo chromosomes with a parental memory



Rachel and Jacob

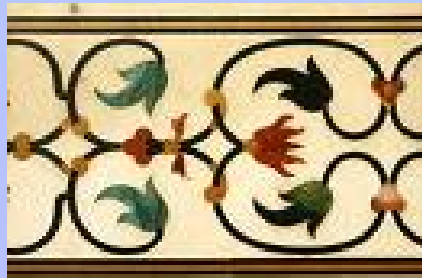
The Book of Genesis

Rachel went into a labor with her second son, Benjamin. The midwife tells her in the middle of the birth that her child is a boy because the labor is difficult.

**Animal reproduction is accomplished
with inconvenience to the mother,
tenacity of the fetus, and cooperative
ingenuity between the two.**

Burwell and Metcalfe
Heart Disease and Pregnancy

Thank You



Eve and Athena were *full grown females*
born from *male progenitors*.

Aphrodite was a *full grown female* born from
Uranus castrated genitals in the spume of
the sea.

The father is the true parent.

Pseudocyesis



Occurrence rate is 1 to 6 for every 22,000 births.
Cause is unknown. Every sign and symptom of pregnancy has been recorded in these patients except the fetal heart beat, the ultrasound image of a fetus, and delivery.



Caenorhabditis Elegans

In just 12 hours, a fertilized egg of this tiny soil-dwelling worm changes from one cell to over 500, neatly arranged into body structures.

Ideas of Gestation and Genetics



Aristotle (326 BC) proposed the genetic principle that physical traits are transmitted by parents. However, he taught that “the human embryo is formed by the male element, and is hatched in coagulated menstrual blood of the female uterus.” When the sperm dominates the maternal substance, a son arises. When the sperm is suppressed, a daughter is born.

The Egyptian Birthing Stool

15th – 20th Century B.C.



Maternal Cyanosis



Dysmaturity



Paternal Aortic Coarctation

Normal Offspring



The Pelvis

A triumphal arch under which we
all must pass

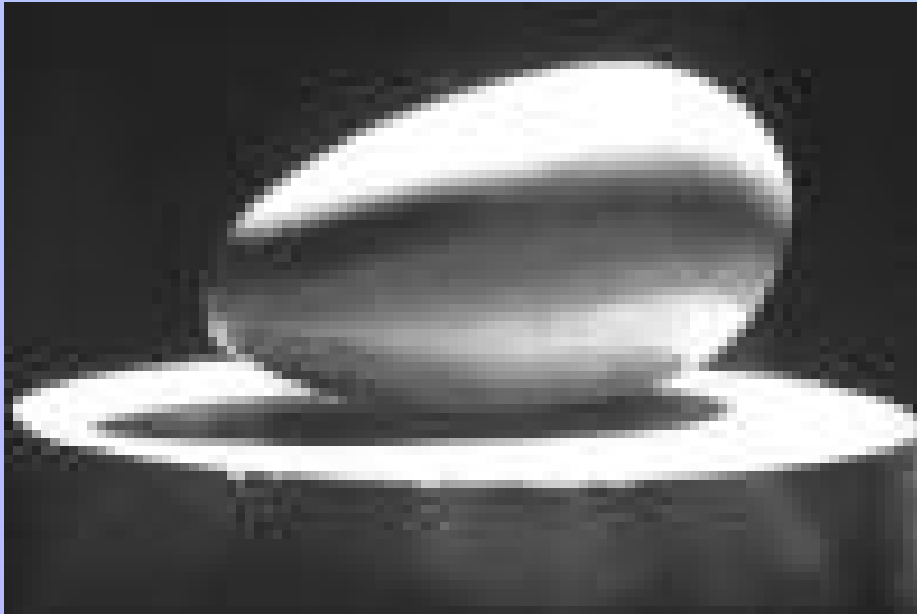


Pregnancy in Congenitally Corrected Transposition

- Three patients, one pregnancy each
- One patient, two pregnancies
- One patient, three pregnancies
- Two patients, five pregnancies each

Total: *7 patients, 17 pregnancies*

Constantin Brancusi



The Beginning of the World



The Newborn

Malpighi established the function of the uterine placenta, stating in his *De Pulmonibus*, that “the lungs of fetus were at rest,” and that “a certain mass called the uterine placenta” acted vicariously for the lungs.

The value of marriage is not that adults produce children, but that children produce adults.