Cancer in Pregnancy; Fetal and Child's Effects

Prof. Gideon Koren MD FRCPC FACMT
Motherisk Israel
Maccabi Research Institute

Cancer in pregnancy

* **1:1000 pregnancies**

  Most prevalent:

* **Breast**
* **Lymphoma**
* **Cervix**

First trimester exposure to chemotherapy

* **Associated with increased risk of congenital malformations (animal and human studies)**
* **Affecting the developing fetus by damaging dividing cells.**
* **Such exposures, which occur mostly when pregnancy was not planned, generally lead to recommendation for termination of pregnancy.**

Exceptions

* **More use of chemotherapy for immunological conditions: SLE, RA, Organ transplant**
* **Azathioprine: Prospective studies failed to document risk of cong. defects**
* **Methotrexate: Cases of skeletal and face malformations;**

Prospective study: more malformations than among controls

Variability in fetal exposure

* 29-year-old pregnant woman with ALL
* Daily cyclophosphamide treatment .
* Delivered a male twin with multiple congenital abnormalities.
* Papillary thyroid cancer at 11 years of age.
* Stage III neuroblastoma at 14 years of age.
* His sister twin was unaffected and exhibited normal development.
* First trimester exposure to cyclophosphamide- major malformations in animal studies and case reports.

Exposure (2)

* **Metabolites of cyclophosphamide are teratogens and carcinogens in animals.**
* **Differences in placental or fetal hepatic cytochrome P-450 may account for the variability in response between the twins.**
* **Disparity between the twins due to differences in metabolite inactivating enzymes.**
* **The risk of second malignancies caused by alkylating agents such as cyclophosphamide has been well documented.**

Beyond the first trimester

* **After 12 weeks of gestation -all fetal organs have completed their embryogenesis (except for the brain),**
* **Fetal risks of chemotherapeutic agents are less clear**
* **May be associated with functional toxicity to the fetus,**
* **Relatively scarce information exists on the transport and fetal effects of anticancer drugs during the second and third trimester of pregnancy.**

Amant *N Engl J Med 2015*

* 129 children in the study,
* 96 exposed to cancer chemotherapy in fetal life .
* Birth weight <10th percentile in 22.0% in the chemotherapy-exposed group
* 15.2% of the control neonates.
* No significant effect of chemotherapy on cognitive development as (Bayley test) (P=0.08),
* Gestational age at birth correlated with the cognitive outcome
* Preterm infants having lower IQ.
* Cardiologic evaluation among 47 children at 36 months of age showed normal findings

Amant (2)

* **This study suggests that prematurity is correlated with worse cognitive outcome, independent of cancer treatment.**
* **Favorable outcome: due to limited exposure to chemotherapy**
* **There may be a functional placental barrier protecting the fetus after the first trimester of pregnancy.**

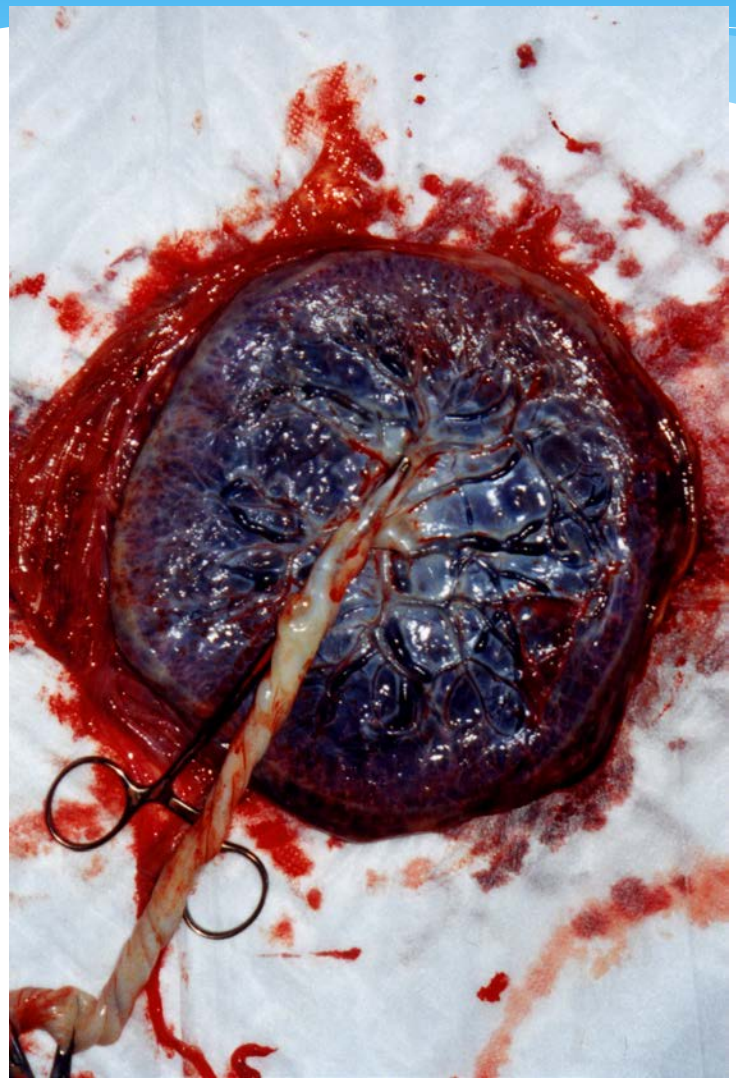
Placental P Glycoprotein

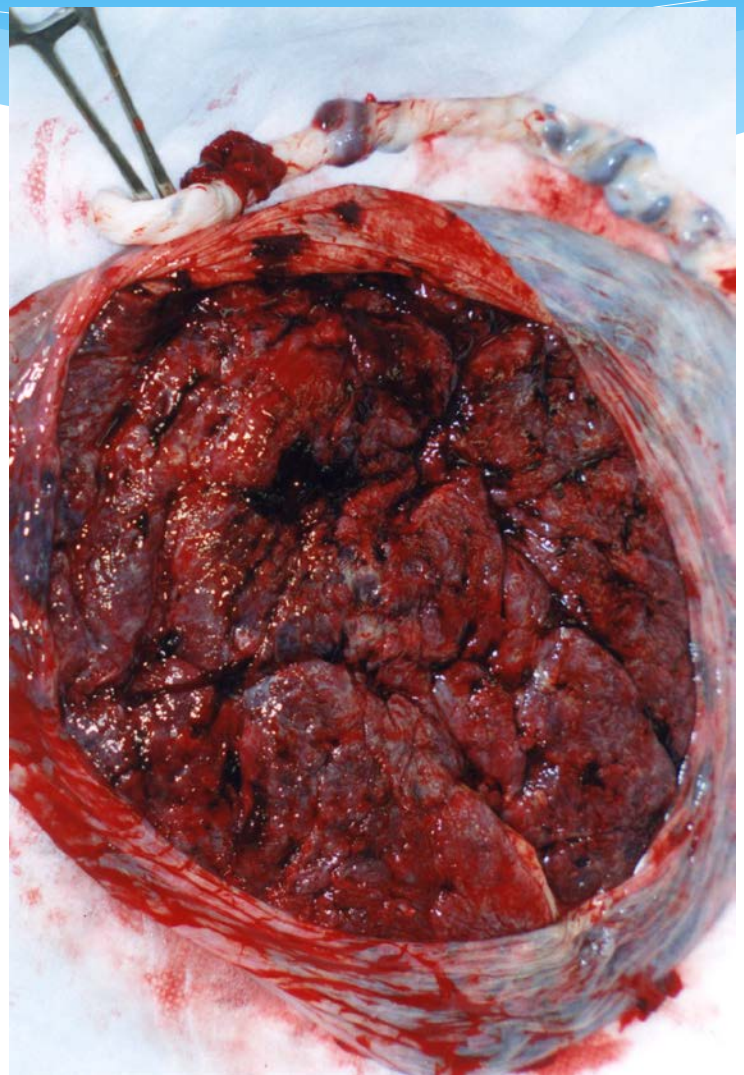
* P-gp substrates are effluxed by placental Pgp
* e.g. daunarubicin concentrates to a much greater extent in fetuses of P-gp (MDR1 a/b) knockout mice [19].
* Fetuses of spontaneously mutated CF1 mice, which lack the placental mdr1a gene (i.e. do not express P-gp in their placenta) -- much more sensitive to birth defects caused by the P-gp substrates

Amant (3)

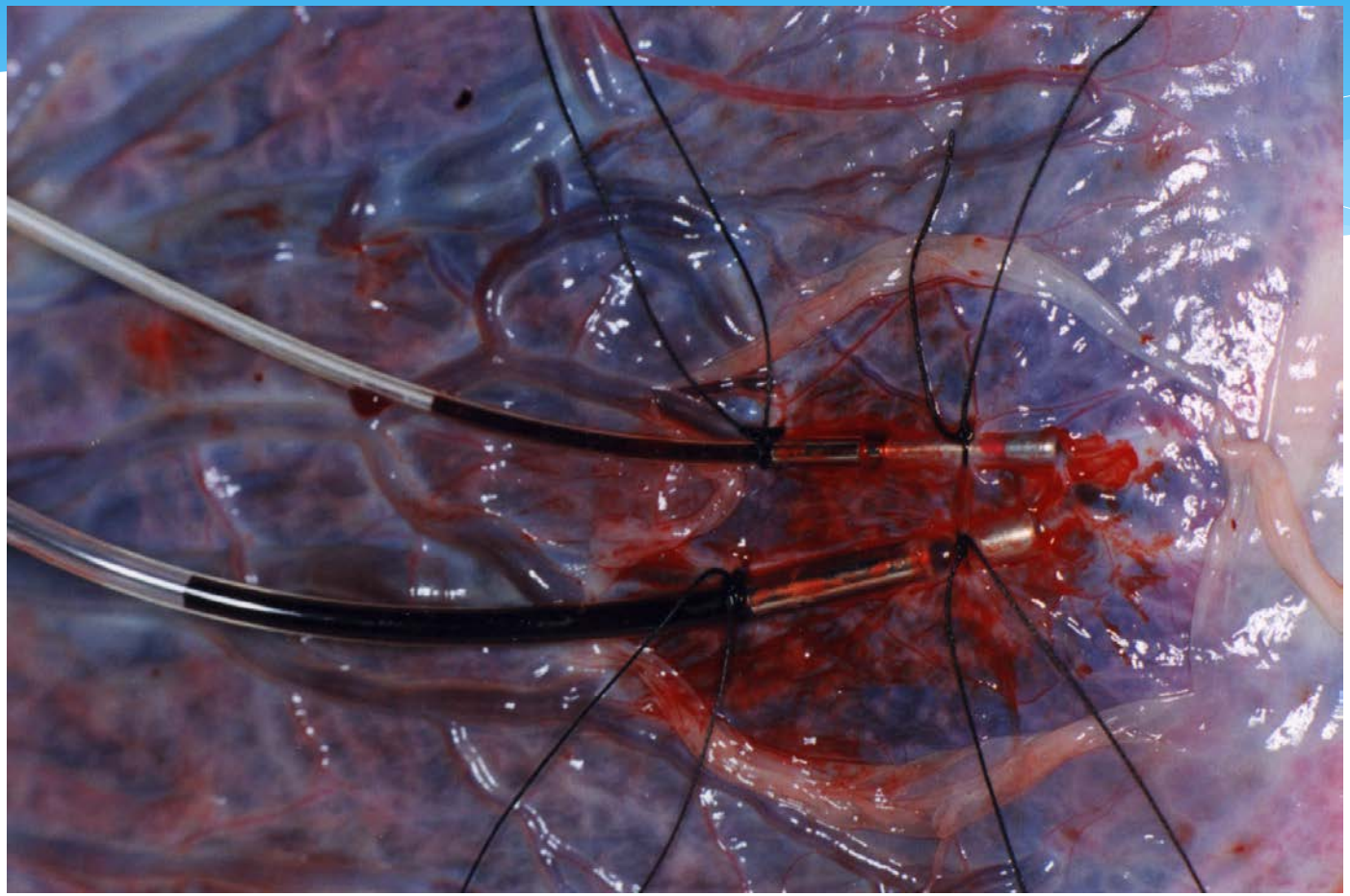
* **Amant et al strongly suggest that the clinical routine practice of "hiatrogenic prematurity" whereby babies are delivered earlier to allow intense maternal chemotherapy, is wrong, as**
* **The damage of prematurity appears to be more serious than the relative fetal safety of the chemotherapy.**

Placental Perfusion(1)

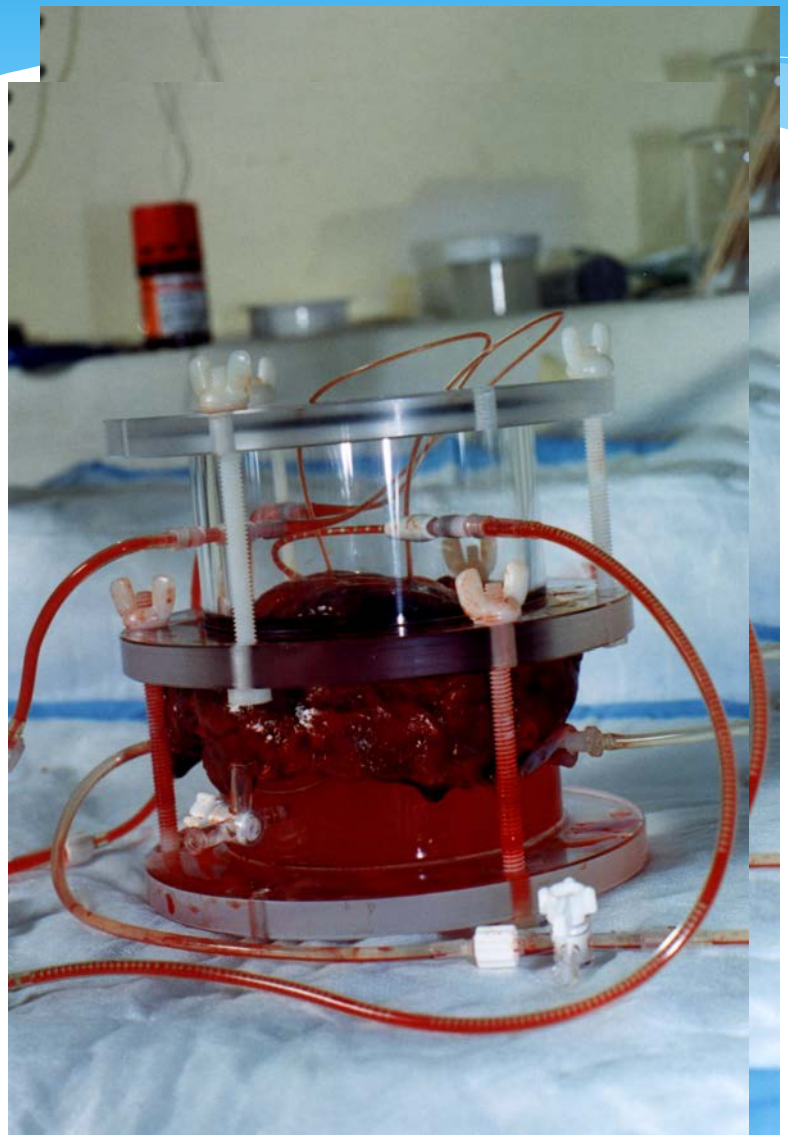


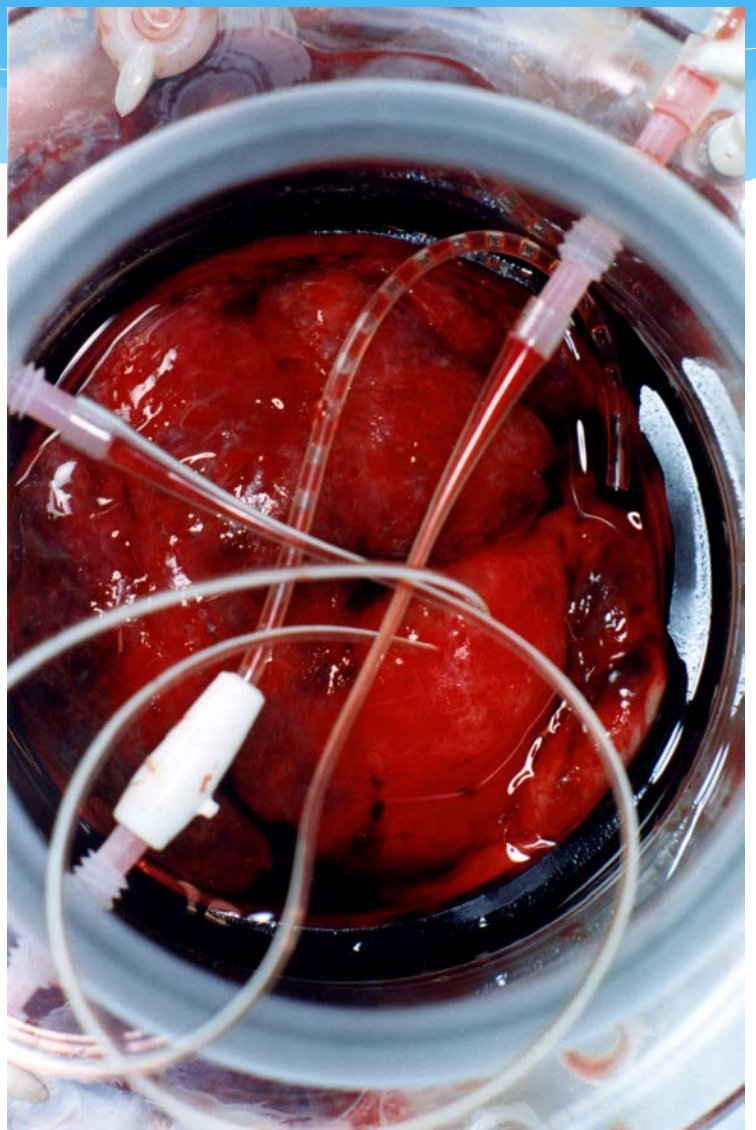


Placental perfusion (2)

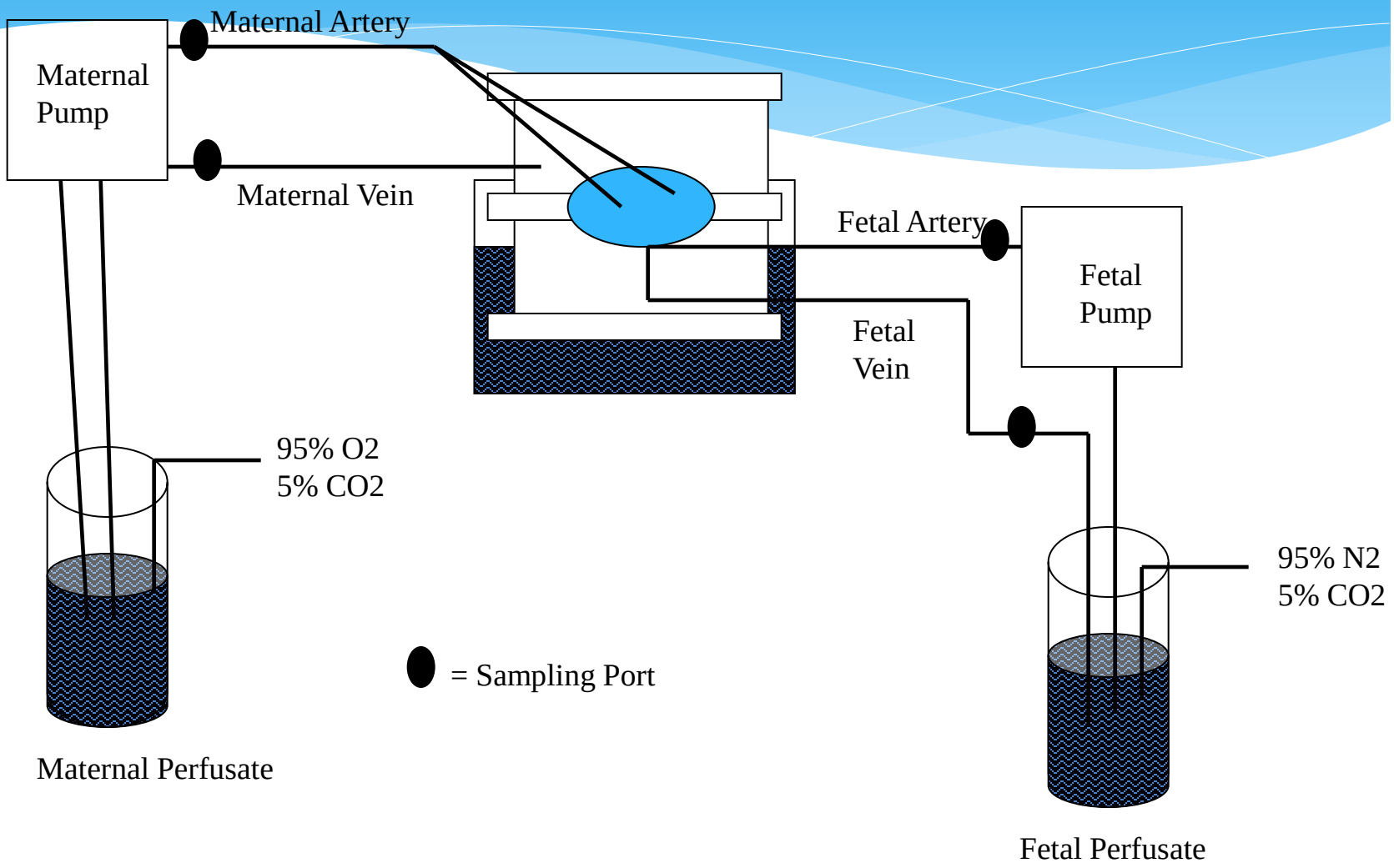


Placental perfusion(3)





Perfusion System



Placental perfusion with taxanes

* **Term placentae were perfused with paclitaxel or docetaxel at 2 different albumin concentrations**
* **. Mean fetal transfer rate of paclitaxel decreased significantly from 5.67 % at low albumin to 1.72 % in physiological albumin conditions.**
* **Overall, the trans placental transfer and placental accumulation of paclitaxel and docetaxel was low and similar**
* **This study highlights the important role of protein binding on drug transfer across the placenta,**
* **Only unbound drug is available for transfer. Taxanes have extensive protein binding (95%)**

Platinum

* Perfusion studies: Transport fractions for carboplatin at low and high concentrations were 0.05 and 0.10, respectively.
* Kohler : 21 patients with cervical cancer diagnosed in their second trimester.
* Received platinum-based chemotherapy at the time of delivery by cesarean section.
* 22 healthy babies without renal, hepatic, auditory, or hematopoietic impairment were delivered.
* Platinum concentrations in umbilical cord blood and amniotic fluid were 23-65% and 11-42% of the maternal blood, respectively.
* Reassuring re fetal safety, although fetal levels were as high as two thirds of maternal levels.

Studies in Baboons

* **Van Calesteren : transplacental transport of commonly used anticancer agents in a pregnant baboon model**
* **Paclitaxel, docetaxel, carboplatin, and trastuzumab were administered at gestational age of 117 days.**
* **After ending the infusion, paclitaxel was not detectable in fetal tissues, whereas, after 3 hours, fetal tissues contained 15% of maternal tissue concentrations.**
* **In contrast, docetaxel could not be detected in fetal blood samples. In the first 3 hours after docetaxel infusion. The transplacental transfer of trastuzumab was 85.0% and 3.0%, 2 and 26 hours a**

Apparent safety of fetal exposure to cancer chemotherapy

* **The apparent favorable outcome of fetuses exposed to chemotherapy after the first trimester :**
* **May be partially explained by the decrease in maternal drug exposure due to:**
* **Larger body weight and volume of distribution, enhanced hepatic and renal clearance of many of these agents in the second part of pregnancy**

Anti cancer chemotherapy	Carboplatin	Higher Vd	Lower Cmax, Lower AUC	Higher Cl
	Cisplatin	Higher free fraction (after 8h)	N/A	N/A
	Epirubicin	Higher Vd	Lower Cmax, Lower AUC	Higher Cl
	Paclitaxel	Higher Vd	Lower Cmax, Lower AUC	Higher Cl

Counseling

* **Woman's health should prevail.**
* **Team work: Oncology, high risk OB, neonatology, psychology, social work, clergy,**
* **Important to ensure that the woman and her family understand maternal and fetal risk-benefit of postponing chemotherapy.**
* **Typically: first trimester diagnosis of maternal cancer= Termination**
* **Second and third trimesters- much less apparent fetal risks**
* **Avoid hiatrogenic prematurity**