FIRST SESSION: **GUEST LECTURE**

Drugs affecting the fetus and Newborn Infant

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Discussion

DRUGS AFFECTING THE FETUS & NEWBORN INFANT

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When prescribing in pregnancy and for the newborn every clinician has to be aware of the potential harmful effects as well as the benefits of the drugs which he administers.

Prescribing during Pregnancy:

The effect that a drug given to the mother will have upon the fetus depends upon a number of factors (Table 1).

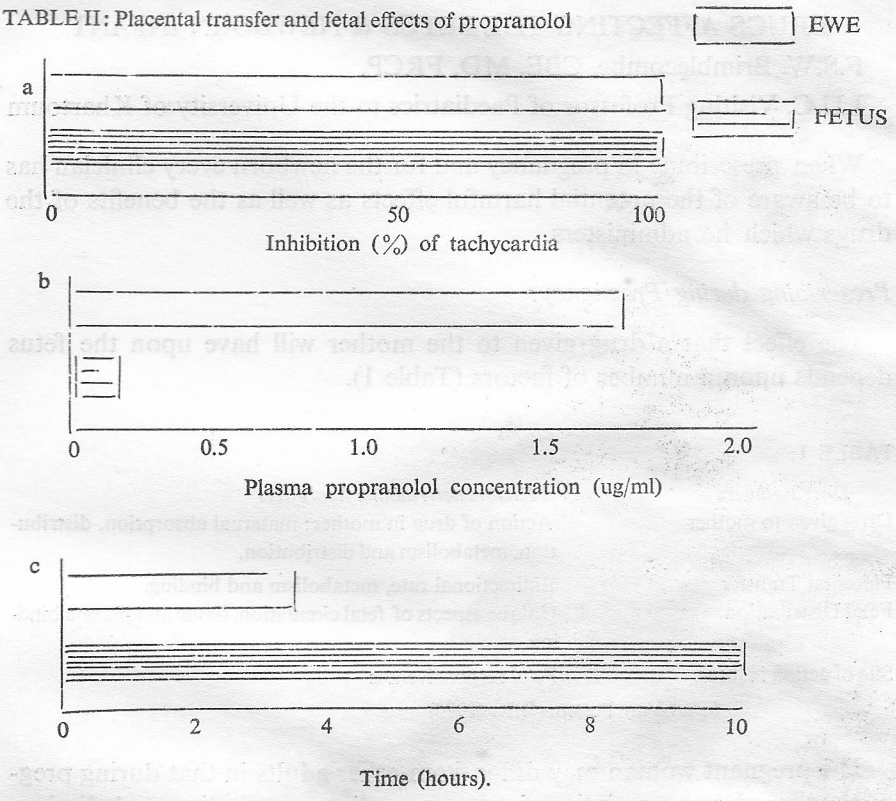
TABLE I:

Drug Pathway	*Factors determining fetal effect*
Drug given to mother	Action of drug in mother: maternal absorption, distribution, metabolism and distribution.
Placental Transfer	Bidirectional rate, metabolism and binding.
Fetal Distribution	Unique aspects of fetal circulation, tissue and plasma binding.
Site of action in fetus.	Fetal responsiveness

(after Van Petten, G.R. (1975)

The pregnant woman may differ from other adults in that during pregnancy there may be variations in the absorption, metabolism and elimination of drugs, particularly when the pregnancy is complicated by hyperemesis, diabetes, nephritis or toxaemia of pregnancy,Drugs given to control hypertension either for nephritis, essential hypertension or toxaemia of pregnancy may be modifying maternal cardiac output or by causing vasoconstriction have secondary effects upon the placental circulation and thus upon the fetal circulation. These effects are difficult to detect in the human in whom the scope for experimental measurement is obviously limited, Examples from animal work indicate the major effects upon the fetal circulation that may result from the prescription of hypotensive agents to the mother. Table II (fromTunstall 1969) and Table III(from Truelove, Van Petten and Willes 1973) indicate the marked variation that may occur in the fetus when β- adrenoceptor blocking agents are given to the pregnant ewe. In sheep propanolol clearly has a much more prolonged effect upon tachycardia in the fetus than in the mother despite the fact that the plasma propanolol concentration is far lower. It is also clear that in sheep there is a marked variation in the effect of other β- adreno-

TABLE II: Placental transfer and fetal effects of propranolol



(a) inhibition (%) of tachycardia produced by isoprenaline (1 ug/kg body wt.) given 30 min after administration of propranolol (1mg/kg body wt.) to the ewe.

(b) peak plasma concentration of propranolol, following administration of propranolol (1 mg/kg body wt.) to the ewe.

(c) duration of inhibition of isoprenaline-induced tachycardia (1 ug isoprenaline/kg body wt.) produced by administration of propranolol (1 mg/kg. body wt.) to the ewe.

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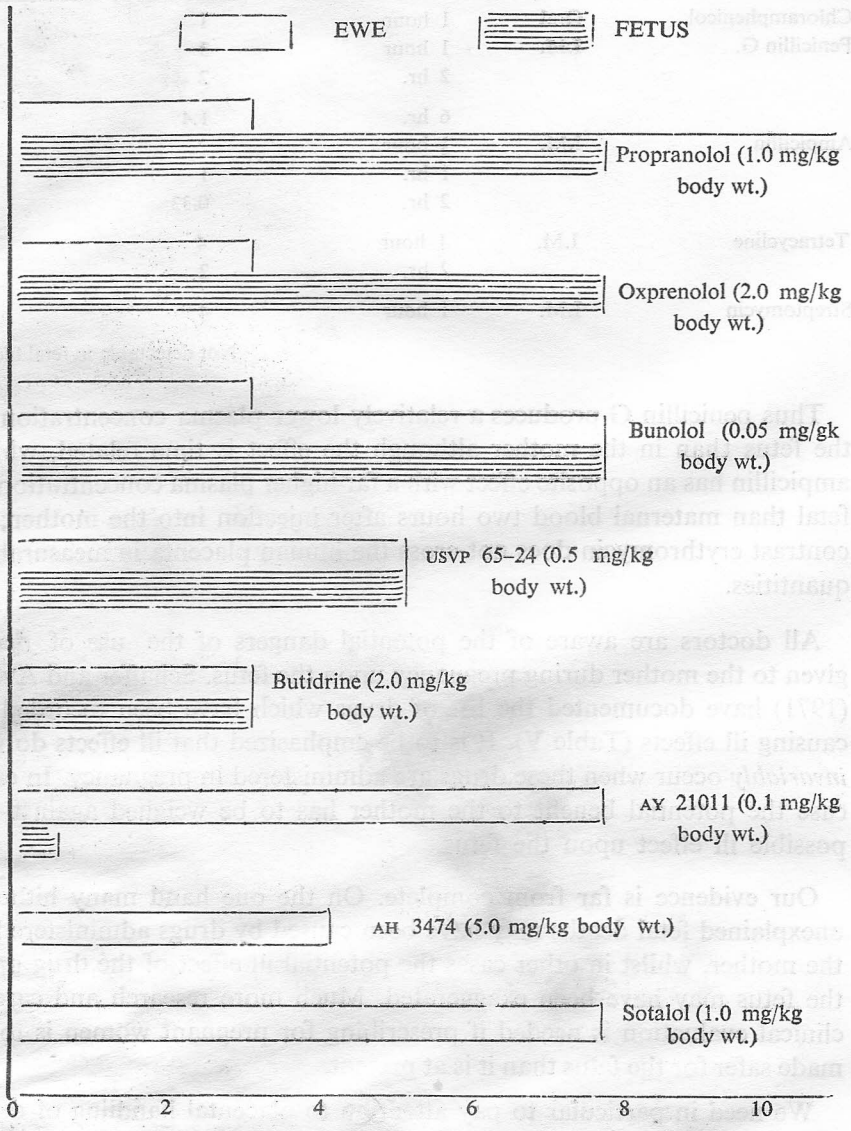
ceptor blockaders some similar to propanolol, others such as sotalol having little or no effect upon the fetus. It is also clear that it would be fallacious to assume that drug transfer across the placenta is identical in the sheep and the human.

TABLE III: Duration of B–adrenoceptor blockade after administration of various drugs to the mother



ANTIBIOTICS:

The placental transfer of antibiotics in the human is also extremely variable (Sereni and Principi 1968). as shown in Table IV.

TABLE IV :

Antibiotic	Route	Time after administration	Maternal Fetal ratio
Chloramphenicol	Oral	1 hour	1
Penicillin G.	I.M.	1 hour	3
		2 hr.	2
		6 hr.	1.4
Ampicillin	I.M.	½ hour	2
		1 hr.	1
		2 hr.	0.33
Tetracycline	I.M.	1 hour	4
		2 hr.	2
Streptomycin	I.M.	1 hour	4

Not detectable in fetal blood

Thus penicillin G produces a relatively lower plasma concentration in the fetus than in the mother although the effect is time related, whilst ampicillin has an opposite effect with a far higher plasma concentration in fetal than maternal blood two hours after injection into the mother; in contrast erythromycin does not cross the human placenta in measurable. quantities.

All doctors are aware of the potential dangers of the use of drugs given to the mother during pregnancy upon the fetus. Schaffer and Avery (1971) have documented the list of drugs which have been recorded as causing ill effects (Table V). It is to be emphasized that ill effects do not *invariably* occur when these drugs are administered in pregnancy. In each case the potential benefit to the mother has to be weighed against the possible ill effect upon the fetus.

Our evidence is far from complete. On the one hand many hitherto unexplained fetal deaths may have been caused by drugs administered to the mother, whilst in other cases the potential ill effect of the drug upon the fetus may have been exaggerated. Much more research and careful clinical evaluation is needed if prescribing for pregnant women is to be made safer for the fetus than it is at present.

We need in particular to pay attention to placental handling of drugs and to the unique pattern of the fetal blood circulation. The placenta treats certain substances such as water by simple diffusion,others such as monosaccharides by selective diffusion.Thus if the maternal side of the placenta is perfused with a solution containing equal parts of glucose and fructose

TABLE V: Drugs given to the mother which may affect the fetus

DRUG	EFFECT
Amethopterin	Abortion, Congenital defect
Ammonium Chloride	Acidosis
Androgens	Masculinization
Barbiturates	Bleeding
Chloramphenicol	Stillbirth (due to grey syndrome)
Chloroquine	Deafness, mental retardation
Chlorothiazide	Potassium depletion
Cortisone	Congenital malformations
Dicoum arol	Bleeding
Smoking (Nicotine)	Impaired fetal growth
Hexamethonium bromide	Paralytic ileus
Iodides	Goitre
Naphthalene	Haemolysis in G-6-PD affected fetuses.
Novobiocin	Hyperbilirubinaemia
Propylthio uracil	Goitre
Progestins	Masculinization
Quinine	Thrombocytopenic purpura
Reserpine	Nasal congestion
Salicylates	Bleeding
Stilbestrol	Masculinization
Streptomycin	Deafness
Sulphonamides	Kernicterus
Sulphonylurea	Congenital malformation
Testosterone	Masculinization
Tetracycline	Inhibition of bone growth, staining of teeth
Thalidomide	Phocomelia
Thiazide diuretics	Thrombocytopenic purpura
Tolbutamide	Congenital malformations
Vitamin D	Hypercalcaemia
Vitamin K	Haemolysis, hyperbilirubinaemia.

there will be a tenfold diffusion of glucose as against fructose into the fetal circulation. Electrolytes, sodium, potassium, calcium, phosphate and magnesium are handled by an active transport mechanism whilst, the transfer of lipids is very variable. We need to consider the pharmacological content of a drug in determining whether or not it will be likely to be concentrated in the fetus when given to the mother. By contrast heparin and erythromycin do not cross the placenta in measurable quantities.

The unique feature of the fetal circulation is that blood passes directly from the placenta via the umbilical vein to the right side of the heart and thence directly to the brain. Thus the usual dilution of a drug whether given orally or by intramuscular injection before it reaches the heart or brain does not occur. Even with intravenous injections in the adult,

substances after passing through the right side of the heart will be diluted in the pulmonary vascular bed before returning to the left side of the heart and then entering the brain. In summary a drug crossing the placenta goes undiluted direct to the fetal heart and brain, a quite different state of affairs to that which occurs in the child or adult.

Drugs affecting the Newborn :

The newborn is immature – the pre-term infant even more so. This physiological difference from older children and adults must never be forgotten when prescribing for the neonate. Three examples serve to illustrate this point.

(a) *Glucuronic conjugation.* Many lipid-soluble compounds require to be conjugated with glucuronic acid before they can be excreted. Much of the hyperbilirubinaemia of the newborn is due to immaturity of this mechanism. The "grey-baby" syndrome caused by the prescription of chloramphenicol (in what would be an appropriate weight for weight dosage for older children) to newborn infants is also due to this same immaturity.

(b) *Glucose-6-phosphate dehydrogenase.* Certain infants, more commonly negro than Caucasian, are prone to develop haemolysis due to an inherited deficiency of G–6–PD when treated with nitrofurantoin, primaquine, Vitamin K or naphthalone containing compounds.

(c) *Renal tubular function.* Electrolyte homeostasis is precarious in the newborn due to immaturity of renal tubular function. Thus hypernatraemia can follow the ingestion of what is to the newborn an excess of sodium and high plasma concentrations can also occur with potassium, phosphate and high levels of blood urea from a high protein intake because of inadequate elimination by the kidneys. In the case of phosphate, the high concentration of this substance in cows milk leads not only to hyperphosphataemia but to secondary hypocalcaemia in the neonate.

Awareness of neonatal immaturity is always an important constraint when planning treatment for the newborn.

Antibiotics :

The ability of newborn and pre-term infants to handle antibiotics also discloses important differences from older children and adults.

TABLE VI: Serum Half-life of Antibiotics in Newborn and Premature Infants

Antibiotic	*Maturity*	*Age*	*Half life of antibiotic in hour*
Chloramphenicol	Pre-term	1 day	15–22 hours
	Pre-term	14-21 days	8–15
	Children	5 years	4
Streptomycin	Pre-term	1– 7 days	7
	Adults	–	2– 3
Kanamycin	Pre-term	0– 2 days	18
	Pre-term	7–21 days	6
	Adults	–	2
Ampicillin	Pre-term	3– 6 days	4– 3
	Pre-term	21–42 days	2
	Term infants	0–24 hrs.	3– 4
	Term infants	2– 7 days	2
Flucloxacillin	Pre-term	1– 7 days	1– 2
	Pre term	21 days	1
	Term infants	1– 7 days	1– 2
	Children	1 year	1
	Adults	–	0.5–0.8
Neomycin	Pre-term	1–10 days	5– 6
	Pre-term	10–21 days	3– 4
Colistin	Pre-term	4– 6 days	2– 3
	Pre-term	7–21 days	2
	Term infants	1 day	9
	Term infants	4– 6 days	2– 3
Cephaloridine	Term infants	1 day	5– 6
	Term infants	4 days	3– 4
	Term infants	10–14 days	2
	Term infants	2– 4 months	1

(After Sereni and Principi (1968)

Anaesthetics and Analgesics :

Oversedation of the newborn or by drugs given to the mother shortly before delivery has serious implications. Initiation of respiration at birth can only be achieved by a vigorous infant. Maternal over-sedation is therefore a critical cause of asphyxia neonatorum. This applies with all anaesthetic and analgesic drugs given to the mother. Even local anaesthetics given for epidural procedures enter the maternal bloodstream, cross the placenta and can affect the fetus (Dunn and Richards 1976).

Currently the motherchild interaction at birth, the bonding process, has been much discussed. For this to take place effectively both mother and child need to be fully conscious and to be able to interact. Failure either by the mother or the child to respond as a result of oversedation inhibits and diminishes the normal interaction between them (Klaus and Kennell 1976) during the first 48 hours after birth.

The now world wide prevalence of drug addiction, when it involves the pregnant woman, may lead to withdrawal symptoms in the newborn particularly in the case of pregnant women on 'hard' drugs.

Drugs excreted in Breast Milk :

Most drugs given to the mother are excreted in breast milk and thus affect the suckling infant (Table VII). Only a few examples are given to indicate the wide range of pharmaceutical preparations that can affect the infant by this means.

Conclusion :

As with every aspect of medical care, a balanced decision has to be made when prescribing for the pregnant woman or for the newborn infant. On the one hand therapeutic necessity may overide the potential ill effect on the fetus or newborn which may in any case be minimal in some of the examples that have been mentioned. On the other hand, there is probably no drug which is harmless and which if used indiscriminately may not give rise to ill effects. Even penicillin which may be life saving in septicaemia, if used thoughtlessly for 'prophylactic' pursposes may, for example, encourage the development of antibiotic resistant pathogens in newborn nurseries.

There is much need for further basic and clinical research into the therapeutics of pregnancy and neonatal care.

TABLE VII: Drugs excreted in Breast Milk

Antibiotics	Penicillins
	Streptomycin
	Tetracyclines
	Chloramphenicol
Other Antibacterials	Sulphonamides
	Nitrofurantion
Sedatives and Hypnotics	Barbiturates
	Phenytoin
	Bromides
Anti-thyroid drugs	Thiuracils
Anti-coagulants	
Anthorquinones	
Vitamin D	
Oral contraceptive drugs	
Antimetabolites	
Hormones	
Purgatives	
Analgesics	Salicylates
Diuretics	Thiazides
Miscellaneous	Radioactive agents
	Atropine
	Caffeine
	Metronidazole
	Qicotine.

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