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PLACENTAL TRANSFER OF DRUGS

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The fetus is not an isolated individual; he lives entirely dependent upon the orderly passage of nutrients and oxygen from the mother and a return of catabolites to her. Along such physiological pathways go most drugs which enter the mother's circulation. A few may shift more slowly than others but eventually most will arrive in the fetal tissues in varying concentrations. While the majority of substances exchanged go from the placental bed across the placental membranes and into the fetal blood, a small amount is secreted from the maternal blood through the amniotic and chorionic membranes into the amniotic fluid; there they are swallowed by the fetus and absorbed into his blood.

FACTORS AFFECTING TRANSFER: PLACENTAL DIFFUSION

The majority of drugs that cross the placental and amniotic membranes do so by diffusion at a rate characterised by Fick's diffusion equation:

$$\text{Rate of Diffusion of Drug} = \text{Placental Surface area} \times \text{Constant} \times \frac{\text{Difference in concentration maternal and fetal plasma}}{\text{Membrane thickness}}$$

In this equation the rate of diffusion of the drug is related to:

1. The placental surface area.

At the beginning of pregnancy, the exchange surface is very much bigger than the embryo for trophoblast covers the whole surface of the growing amniotic sac. As pregnancy proceeds, the area of the amniotic sac involved is reduced to that of the developed placental disc; the surface area of the placenta itself is greatly enlarged by the numerous folds and villi. Aherne and Dunnill (1966) have calculated that the surface area rises from 5 sq.m. (28 weeks) to 11 sq.m. at term, about 120 sq. ft, the floor area of a moderately sized bedroom.

2. The diffusion constant depends upon a group of features:

The molecular weight of the drug; generally molecules with a molecular weight below 400 diffuse across very easily, those with molecular weight between 400-700 moderately easily and if the molecular weight is above 700 molecules diffuse with difficulty. Larger molecules than this have difficulty in perfusing along biochemical gradients. As the molecular weight increases, so lipid solubility becomes an even more important factor.

The space formula of the drug, whether it is l- or d- notation; this in turn affects the lipid solubility and the ionic charge of the drug. Fat soluble drugs cross the membranes, themselves made of lipoproteins, more readily than those that are not; nonionised molecules pass more rapidly than those that are charged. The extent to which any drug is ionised is both pH and temperature dependent; while these are fairly constant in the pregnant woman, there can be small changes of pH in prolonged maternal metabolic alkalaemia. The pH of the fetal blood is usually lower than that of the maternal arterial blood, hence the proportion of drug transmitted will be less ionised in the fetal circulation than the maternal.

3. The concentration of a drug measured in maternal blood depends upon the amount ingested and the route by which it has been given. Obviously if the way it has been given allows a high concentration to arise momentarily, for example during intravenous therapy then, there will be a greater transplacental gradient as the bolus of blood with a large amount of drug is being circulated.

The total amount of drug in the blood is less important than the amount actually available for transfer – the free drug. This consists of the drug not carried in the red cells nor bound to protein. Drugs generally bind better to albumin than to globulin; in most women albumin concentrations are lower is pregnancy and in some diseases such as pre-eclampsia they may be further reduced. In such a state the amount of protein available for binding is reduced and the quantity of free drug in the plasma is increased. In any group of antibiotics, the extent of protein binding varies enormously. For example 60-80% of sulphadimidine binds while sulphasalazine hardly binds at all.

4. The membrane thickness varies greatly as pregnancy proceeds. In early pregnancy, the villi are quite plump with a diameter of 150-200 μm and the blood vessel containing the fetal blood is in the centre of the villus, separated by a con-

siderable amount of trophoblastic tissue from the surface of the villus where the maternal blood is found. This can be a distance (or effective membrane thickness) of 20-40 μm. By 40 weeks gestation the villi have a diameter of about 40 μm and the fetal vessels are forming a thinner walled web nearer the surface. They are covered by only a thin syncytotrophoblast which is even more irregularly thinned into localised domes so that in some places the blood vessels come close to the surface; the effective membrane thickness is thus reduced to only 2 μm. The relationship of placental membranes to transfer is well reviewed by Fox (1979).

FACTORS AFFECTING TRANSFER: PLACENTAL AND FETAL

As well as the physico-chemical factors, the supply of drug available for diffusion from the maternal side of the placenta will depend upon blood flow to the placental site. Cardiac output is increased in pregnancy and the major part of the blood (85-90%) arriving at the uterus goes to the placental bed. However, flow may also be diminished acutely by the uterus pressing on the aorta and pelvic vessels or it can be chronically altered by changes in the blood vessels in diseases such as pre-eclampsia. Whilst normally, the spiral arteries which open into the placental bed funnel widely at their ends so that blood jets out readily, in pregnancy associated hypertension this funnel is narrowed and placental bed flow can be reduced by as much as 40%. In the placenta itself some drugs are actually metabolised so that a variable amount actually reaches the fetus. This factor is not a major one in antibiotics.

Having reached the fetal circulation the handling of drugs may differ entirely from that in the mother. Fetal blood is relatively acidotic with an arterial pH of as low as 7.25 compared with a pH of 7.45 in maternal blood. There is also a high fetal haematocrit level with more red cells per unit volume to take up the drug which is then lost for immediate perfusion. There are differences in the characteristics of the fetal serum proteins and so of drug binding. The circulation pattern of blood in the fetus means that on arrival back from the placenta, in the umbilical vein, much of it travels in the ductus venosus so the drug bypasses the fetal liver and enters the heart directly. It is thus not dealt with in that organ which is normally an important drug metabolic and storage area, and is not acted upon by hepatic enzymes before it arrives in the fetal tissues. In early pregnancy the fetus has little fat in tissues but from 30 weeks of gestation onwards, subcutaneous adipose tissue is laid down and this absorbs a certain amount of any lipid-soluble drugs.

All these variables make it impossible to predict with any accuracy the concentration of a given antibiotic which will pas into and be effective in a fetus.

FACTORS AFFECTING TRANSFER: MATERNAL

Many mothers take antibiotics in pregnancy; Doering and Stewart (1978) showed that 21% of pregnant women surveyed by them received an antibiotic. These drugs are widely used by doctors as the first line of defence against a variety

of infections which the mother may contract, either incidental to or because of the pregnancy. When given to a mother-to-be by the route usually used for that antibiotic, the maternal serum levels are lower than in the non-pregnant woman because of the larger intravascular and extracellular volume which dilutes the drug (up to 40% increase in volume by 20 weeks gestation). There is also an increase in the glomerular filtration rate and the hepatic biotransfusion capacity so there is an increased excretion rate. Finally the very transfer of the drug to the fetal compartment means that a further variable amount is lost to the mother and so reduces concentrations of circulating antimicrobials.

All antibiotics cross the placental membranes to some degree, their passage being determined by the principles laid down in the first part of this chapter. Very few have known toxic effects on the fetus or are teratogenic when given at the crucial period in the early weeks of pregnancy. However, this is not always certain and it would be wise therefore to avoid the use of a new antibiotic in the first ten weeks of pregnancy until organ systems are formed. The testing of such drugs may have relied upon untoward reactions in species other than man. As Osler said "Be not the first, nor the last to try a new treatment". This applies to all new drugs in early pregnancy including the antibiotics.

THE ANTIMICROBIAL AGENTS USED

The placental transfer of some groups of antimicrobial agents used in obstetrics may be considered:

Penicillins and cephalosporins

All penicillins cross the placenta rapidly and easily. The molecular weight of penicillin is 334 and its sodium salt 356; it is not ionised. Hence, therapeutic concentrations appear in the fetus as soon as they do in the mother after a therapeutic dose to the mother. Penicillin enters the amniotic fluid easily and more readily in the latter part of pregnancy. Neither penicillins nor cephalosporins accumulate in the fetus but since fetal renal clearance is decreased, they do persist for a longer time in fetal body fluids.

Aminoglycosides

Aminoglycosides are transferred across the placenta rapidly and soon attain blood and tissue fluid levels about half those of the mother. The molecular weight of streptomycin is 582 and it is not ionised. Gentamicin is rapidly concentrated in the amniotic fluid, probably because the fetal kidney can concentrate this antibiotic and excrete it into the amniotic fluid. In later pregnancy concentrations in the fetal kidney exceed those in maternal serum.

The effect of streptomycin on the eighth nerve is dealt with elsewhere in this supplement. Basically although some ototoxicity has been shown, the alteration in hearing was not in the normal speech range of most children.

Tetracyclines

Placental transfer of tetracyclines occurs readily and these antibiotics achieve a concentration half that in maternal blood when therapeutic doses are given to the mother by the usual routes. There is a tendency for tetracyclines to be concentrated selectively in the bone causing some brown-yellow discolouration. The same effect is found in tooth enamel where it is accompanied by weakness of structure. There is less resistance in extrauterine life; in consequence, caries and tooth discolouration are seen in the deciduous but not the permanent dentition. There is also a slight reversible retarding effect upon bone growth. In consequence, this antibiotic is not used commonly in pregnancy.

Chloramphenicol

This antibiotic has a molecular weight of 323 and is not ionised. It rapidly achieves a fetal blood concentration of about half that of the maternal blood when given in ordinary therapeutic dosage. Whilst from the bacteriological point of view chloramphenicol is an excellent broad spectrum antibiotic, it is associated with bone marrow aplasia and is used infrequently in obstetrics. In the newborn, chloramphenicol administration can be associated with the Grey Syndrome but this is not a feature in the fetus. However, its potential depressant effect on maternal bone marrow would be enough to stop it being used in pregnancy.

Sulphonamides

All the sulphonamides pass readily into the fetus but their protein binding in maternal and fetal blood affects the levels of free drug available. They interfere with folic acid synthesis and compete with bilirubin for sites on albumin. In consequence, there is a theoretical, increased risk of kernicterus and the possibility of haemolysis in G_6PD deficiency. In fact, the former is very rare; the evidence rests upon work in other species and one or two rare cases where mothers had a prolonged and high dosage of sulphonamides. However, the use of these antimicrobial preparations is conventionally avoided in late pregnancy.

Metronidazole

This anti-flagellate and anti-anaerobe antimicrobial may, in theory, interfere with inosinic acid, a nucleic acid precursor. However, it has been used frequently in the treatment of trichomonas infection in pregnancy and more recently for Gram-negative anaerobic infections without any reported side effects (Ledward and Hawkins, 1983).

TREATING THE FETUS WITH ANTI-MICROBIAL THERAPY

The fetus can become infected in the uterus either across the placenta (e.g. syphilis) or through the amniotic fluid (e.g. staphylococcal pemphigus). Staphylococcal, streptococcal and *E. coli* infections of amniotic fluid may occur and the

infected liquor can cause neonatal skin or lung infections. Prolonged rupture of the membranes and repeated vaginal examinations add to risks of these.

It is good practice to consult a paediatrician prospectively about an antimicrobial to be used to treat a fetal infection, for he is going to have to continue therapy to the newborn child after delivery; a continuum of antibiotics should be established by agreement to avoid any gaps in therapy.

Cephalosporins and penicillins crosse the placenta easily and are secreted also by the amniotic membrane into the amniotic fluid. Amoxycillin is the most commonly used. An intravenous injection given to the mother produces a rapid rise in concentration in the maternal serum and leads to a high concentration in the fetal tissues (by placental transfer) and in the amniotic fluid (by amniotic transfer). Subsequent fetal levels would be adequately maintained by maternal intramuscular injections. This antibiotic has a wide range of activity against Gram-negative organisms and a low toxic level to the fetus. Despite the fetus having lived in an antibiotic-rich environment for the last hours of intrauterine life, it is still wise to take swabs from the skin, nose and ear of the newborn child at birth in order to check sensitivity and ensure that the antibiotic used has been the best one to eliminate that infection.

In the middle trimester of pregnancy, despite apparently adequate fetal concentrations of antimicrobial agents to which the organisms are sensitive, fetal response is poor and infection sometimes continues. This is probably more a factor of an immature fetal immunological response than failed antimicrobial therapy.

CONCLUSIONS

The many variables in maternal, placental and fetal metabolism and of placental and amniotic membrane transfer make it impossible to be certain about the precise levels of antibiotic in the fetal tissues. Should a mother have a serious and treatable infection, most obstetricians would use the appropriate agent, bearing in mind the comments made above for certain antimicrobials. An assessment must be made to include the risks to the fetus of an untreated infection continuing in the mother. There may be concomitant pyrexia, bacteraemia and toxaemia, all of which can have a worse effect upon the fetus than the side effects of any antimicrobial agent given. The obstetrician will weigh in the balance risks to the fetus of the antibiotic against the risks of not treating the mother appropriately and then decide the better course of action. In a small number of cases, he might treat the fetus as his primary patient by the indirect route of giving the mother the antimicrobial agent and allowing it to cross to the fetus by the placenta.

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