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Fetal Pharmacotherapy

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Abstract

Rapid progress has recently been encountered in pharmacologically treating the unborn baby. This unique area of drug therapy raises new methodological and ethical questions. This article is a systematic review of known modalities of fetal pharmacotherapy, and aims to highlight essential principles, difficulties and controversies in fetal pharmacotherapy.

Unique pharmacokinetic features of pregnancy, the placenta and the fetus govern maternal-to-fetal drug transfer. Ethically, it is important that the mother and family are appropriately informed about the evidence in favour of specific fetal therapy, its risks and alternatives.

Antenatal use of corticosteroids for lung maturation is an example of adequate methodology, leading to clear results. In contrast, the initial hopes in antenatal use of phenobarbital were based on less than optimal methodology. Folic acid for the prevention of neural tube defects is the first instance of fetal therapy that has led to the prevention of a major malformation. Serious infections, such as HIV, Group B streptococcus and toxoplasmosis highlight the need for controlled, randomised studies to prevent fetal infection.

With scores of new modalities of fetal therapy likely to be introduced in the next few years, it will be important to adhere to the best possible methodology and execution, in order to address optimally the needs of the fetus.

Fetal morbidity can occur in healthy mothers (e.g. fetal arrhythmias), as part of a symptomatic maternal condition (e.g. toxaemia, thyrotoxicosis) or, more often, when the mother has asymptomatic pathology (e.g. toxoplasmosis). Over the last few decades, a rapid progress in prenatal diagnostic techniques was coupled with a move toward preventative therapy. Lack of adequate postnatal treatments for various conditions, initiated during pregnancy, have led to the search for new ways to treat the unborn, thus preventing long-term morbidity or mortality.

Fetal pharmacotherapy entails the introduction of a chemical or biological substance that has the desired pharmacological effect on the fetus, and therefore in its broader definition may include blood products and vaccines. The major focus of the present review is the fetus as the therapeutic target, and therefore on agents given to the mother to reach the fetus, or those injected directly into the fetal compartment (figure 1).

This review cannot cover in a critical manner all forms of fetal pharmacotherapy offered today. Rather, we have chosen to focus on examples which highlight essential principles, difficulties or controversies. Table I presents a comprehensive list of pharmacotherapeutic fetal interventions, and the type of evidence existing for their effectiveness and safety.

1. Methods of Literature Search

We conducted a review of all published articles related to fetal pharmacotherapy using Medline and Embase since their inception and until December 2001. Books and book chapters were also re-

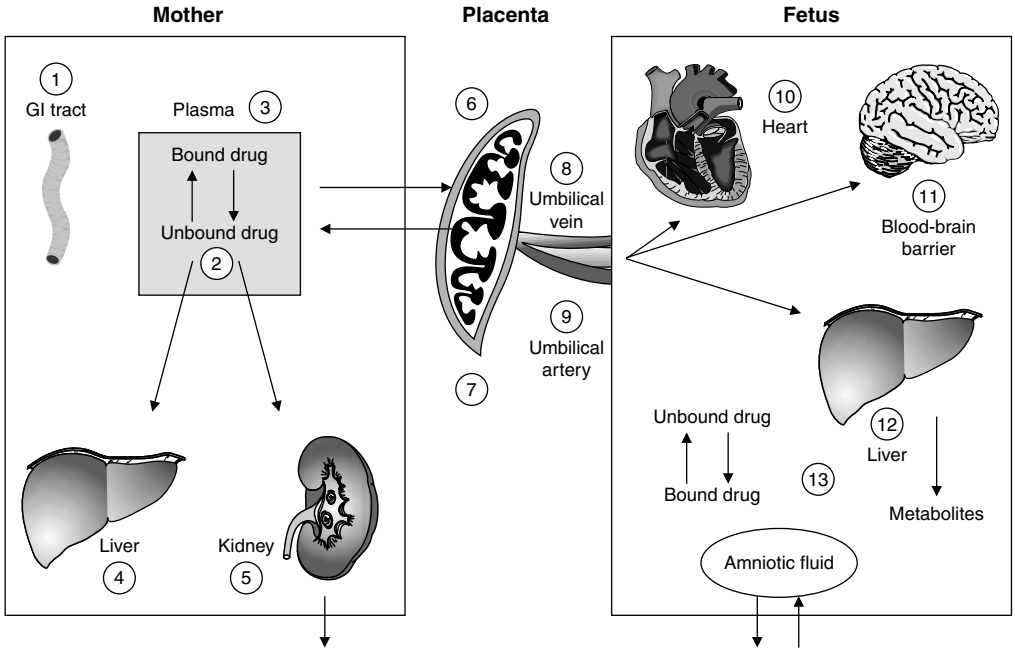

Fig. 1 Drug disposition in the maternal-placental-fetal system. The factors affecting the pharmacokinetics and drug effects on mother and fetus are: **(1)** altered maternal absorption; **(2)** increased maternal unbound drug fraction; **(3)** increased maternal plasma volume; **(4)** altered hepatic clearance; **(5)** increased maternal renal blood flow and glomerular filtration rate; **(6)** placental transfer; **(7)** possible placental metabolism; **(8)** placental blood flow; **(9)** maternal-fetal blood pH gradient; **(10)** preferential fetal circulation to the heart and brain; **(11)** undeveloped fetal blood-brain barrier; **(12)** immature fetal liver enzyme activity; and **(13)** increased fetal unbound drug fraction. **GI** = gastrointestinal.

Table I. Conditions in which fetal pharmacotherapy is or has been used, and the type of evidence that exists to support their use

Condition	Therapy	Adverse maternal/fetal effects of the drug	Type of evidence
Anaemia[1] (alloimmune; parvovirus infection)	Fetal blood transfusion	Fetal infection, PROM, premature labour, haemorrhage, cord tamponade/thrombosis/laceration, umbilical arterial spasm, feto-maternal haemorrhage, GVHD	CS, CC
Arrhythmia[2,3]	Digoxin	Potential maternal toxicity[a]	CR, CS 50% SVT & AF. Hydrops & AF: predictors of poor response
	Procainamine	Potential maternal toxicity, GIT disturbances, fever, lupus, agranulocytosis[a]	CR for AF, SVT
	Quinidine	Maternal cinchonism, maternal QRS & QT prolongation[a]	CR for AF & SVT
	Flecainide	Maternal paresthesia, visual disturbances[a]	CR for AF & SVT
	Propafenone	May aggravate asthma; hypotension, dizziness, blurred vision[a]	CR, partially effective
	Propranolol	May exacerbate maternal asthma or heart failure; hypoglycaemia, IUGR, adverse perinatal effects (hypotension, hypoglycaemia, bradycardia)	CR, mostly not effective
	Amiodarone	No maternal adverse effects described because of brevity of therapy. Concern: fetal hypo- or hyperthyroidism, potential fetal thyroid disturbances	CR, CS
	Verapamil	Maternal bradycardia, aggravation of heart failure; intrauterine death	CR, CS for AF for SVT
Carboxylase synthase deficiency[4]	Biotin		CR
Congenital adrenal hyperplasia[5]	Corticosteroids	Long-term: maternal Cushing's syndrome, hypertension, hyperglycemia; fetal oral cleft (in 1st trimester).	CS
Congenital lupus[6]	Corticosteroids	Long-term: maternal Cushing's syndrome, hypertension, hyperglycemia; fetal oral cleft (in 1st trimester).	CT
Fetal paralysis[7]	Pancuronium bromide, tubocurarine		CS
Goiter[8] (hypothyroidism or hyperthyroidism)	Intra-amniotic thyroxine control of maternal Grave's disease		CT
Group B streptococcus[9]	Penicillin		Meta
Hemolytic anemia[10] (RH incompatibility)	Anti-D		RCT, Meta
Hepatitis B[11]	Heptavax		CoS
HIV[12-15]	Zidovudine with protease inhibitors		RCT, Meta CoS
Hydramnios[16]	Indomethacin	Maternal nausea, heartburn headache, vertigo, tinnitus, antagonism of anti-hypertensive drugs, decreased urinary output, decreased platelet aggregation. Fetal closure of ductus; renal insufficiency, necrotising enterocolitis. Not to be used after 32wk and with caution between 32-34 wks	CS, RCT
Hyperbilirubinemia[17]	Phenobarbital	Potential fetal effects on brain (cognition)[18]	RCT
Hyperthyroidism[19]	Propylthiouracil, thiamazole (methimazole)		CR, CS
Hypothyroidism[20]	Intra-amniotic thyroxine		CR, advantage controversial

Table I. Contd

Condition	Therapy	Adverse maternal/fetal effects of the drug	Type of evidence
Intraventricular haemorrhage[18,21-39]	Corticosteroids	Short-term: infections, attenuated growth[30]	RCT, Meta, CoS
	Phenobarbital	Lowering of IQ[18]	RCT, Meta, no clear efficacy over corticosteroids
	Vitamin K		RCT, inconclusive
Listeria[40]	Ampicillin		CoS
Marosomia (secondary to gestational diabetes)	Insulin	Insulin does not cross the human placenta.	RCT
Methylmalonic acidaemia[41]	Vitamin B_{12} (cyanocobalamin)		CR
Neural tube defects[42]	Folic acid		CC, RCT, Meta
Patent ductus arteriosus[43]	Corticosteroids	Short-term: infections, attenuated growth	RCT
Respiratory distress syndrome[21-29,44]	Corticosteroids	Short-term: infections, attenuated growth	RCT, Meta, Cos
	Thyrotropin releasing hormone (protirelin)		RCT, ineffective
Rubella[45]	Rubella vaccine		Registry
Syphillis[46]	Penicillin		CT
Thrombocytopenia[47,48]	Fetal platelet transfusion		CR
	Corticosteroids	Long-term: maternal Cushing's syndrome, hypertension, hyperglycemia; fetal oral cleft (in 1st trimester)	CR, inconclusive RCT
	IgG (with or without corticosteroids)		CS, RCT
Toxoplasmosis[49,50]	Spiramycin		CS
Varicella zoster[51]	VZIG	Acyclovir	Prospective CoS

a Monitor drug concentrations.

AF = atrial fibrilation; **CC** = case-control study; **CR** = case reports; **CS** = case series; **CoS** = cohort study; **CT** = clinical trial; **GIT** = gastrointestinal tract; **GVHD** = graft *vs* host disease; **Ig** = immunoglobulin; **IQ** = intelligence quotient; **IUGR** = intrauterine growth restriction; **Meta** = meta-analysis; **PROM** = premature rupture of membranes; **RCT** = randomised, controlled trial; **SVT** = supraventricular tachycardia; **VZIG** = varicella zoster immune globulin.

viewed for additional references. The relevant studies were reviewed systematically, the type of study was defined [e.g. randomised, controlled trials (RCTs), registries], the results were tabulated, and methodological strengths and weaknesses were identified.

2. Pharmacokinetics of the Maternal-Fetal Unit

It has been assumed for decades that the placenta serves as a barrier, effectively preventing endogenous or exogenous molecules from reaching the fetus. With the advent of analytical and experimental methods it has become apparent that most medicinal drugs cross the placenta to various extents. During most of the pregnancy, the human placenta has only a single syncytial layer of cells separating the fetal capillary endothelium from the maternal blood. The fetal capillary endothelium is characterised by loose cellular connections and hence it does not pose a hermetic barrier to transport.

Most drug transfer across the placenta occurs by passive diffusion, with the net transfer depending on the diffusion constant (K) of the drug, the surface area available for transfer (A), the concentration gradient between the mother (Cm) and the fetus (Cf), and the thickness of the placental membranes (X) according to Fick's equation:

$$\text{rate of diffusion} = K \bullet A\,(Cm - Cf)/X$$

In addition to passive diffusion, endogenous molecules such as glucose are transported by facilitated diffusion, which is carrier-mediated but not energy-dependent. Facilitated diffusion of a chemical would enable it to reach higher peak concentrations in the fetus than would be expected by simple diffusion. Another form of placental transfer is energy dependent active transport, such as the one responsible for the placental transfer of amino acids, which maintain higher fetal than maternal concentrations. Nicotine and cocaine have been shown to inhibit amino acid transport across the placenta, as a possible cause of intrauterine growth restriction.[52] Several medicinal molecules that are analogues of endogenous compounds have been shown to be transported by active transport, including methyldopa and fluorouracil.[53,54]

Recent work has shown the importance of the placental multiple drug resistance pump (*mdr*) p-glycoprotein in inhibiting placental transfer of cytotoxic agents. In mice lacking placental *mdr* gene encoded for p-glycoprotein or with this pump blocked, substantial increases in fetal exposure to digoxin, saquinavir and paclitaxel have been shown compared with animals that have a full, unblocked pump function.[55]

Consistent with these findings, mice deficient in placental p-glycoprotein exhibited enhanced susceptibility to birth defects induced by p-glycoprotein substrates.[56] Because women use a variety of drugs which are p-glycoprotein substrates (e.g. digoxin, azithromycin) or inhibitors (e.g. cyclosporine, verapamil), inhibition of placental p-glycoprotein may have major effects on fetal exposure to such compounds. This new knowledge may lead to methods that will enhance drug concentrations in the fetal compartment (e.g. digoxin for fetal arrhythmias).

Several factors modify the rate and extent of transfer of a given drug across the placenta, including its physiochemical properties, plasma protein binding, placental blood flow and placental drug binding, as well as pathological processes in the mother or fetus (table II). These have implications for circulating levels in maternal blood. The dose of drug given to the mother has to be taken into account, as it will determine maternal circulating levels.

Table II. Factors modifying drug transfer across the placenta[54]

Modifying factor	Effect	Clinical example
Physiochemical properties	Lipid-soluble drugs cross more rapidly than water-soluble drugs. Ionised molecules cross more slowly. More alkaline pKa of drug - more 'ion trapping' in the more acidic fetus, causing faster transfer	Fentanyl crosses more rapidly than pethidine (meperidine)
Size of molecule	Molecular weight less than 100: rapid transfer Molecular weight up to 1000: slower transfer Molecular weight above 1000: no transfer	Heparin does not cross the placenta and does not exert adverse fetal effects
Placental blood flow	The rate of transfer of most non-ionised, lipophilic drugs depends on placental blood flow	Oxytocic drugs, β-blockers, constituents of tobacco smoke, may all decrease placental blood flow
Protein binding	It is the free (unbound) fraction of the drug that crosses the placenta	Propranolol (highly protein bound) crosses at much slower rate than atenolol (negligible protein binding). Dexamethasone has a low protein binding and is preferable to high protein-bound corticosteroids
Placental binding	Drugs with extensive placental binding may exert more effect on the placenta	Spiramycin concentrates at 5:1 ratio in the placenta, conferring its efficacy in placental toxoplasma infection
Pathological processes	May modify drug transfer	Fetal hydrops and placental oedema decrease transfer of digoxin from mother to fetus, explaining the relative resistance of fetal arrhythmias in fetuses with hydrops
Placental metabolism	May modify drug transfer	Inactivation of prednisolone

Table III. Major pharmacokinetic changes in pregnancy[59]

Change in pregnancy	Pharmacokinetic effect	Potential clinical effect
Larger body weight	Lower serum concentrations	Smaller effects if dose not increased
Lower serum albumin levels	Higher free (unbound) fraction leads to greater transport, clearance	No change in steady state concentration of free drug. e.g. phenytoin
Increased hepatic metabolic rate	Faster clearance of rate of some drugs metabolised by the liver	Smaller effects if dose is not increased e.g. dexamethasone is not metabolised in the liver, and hence is more likely to cross placenta at higher concentrations
Decreased hepatic metabolic rate	Slower clearance rate	e.g. theophylline metabolised more slowly
Higher liver blood flow	Faster clearance rate of high extraction ratio drugs	Smaller effects if dose not increased
Higher glomerular filtration rate	Faster clearance rate of renally excreted drugs or their active metabolites	Smaller effects if dose not increased e.g. lithium, digoxin
Lower compliance (because of fears of teratogenicity)	Lower drug concentrations	More therapeutic failures

Because fetal blood is more acidic (pH 7.3) than the maternal circulation (pH 7.4), weak base drugs are more ionised in the fetal circulation; this 'ion trapping' creates a concentration gradient towards the fetus. Another important mechanism leading to the persistence of drug in the fetal circulation is urinary excretion of drugs into the amniotic fluid, which is swallowed by the fetus and absorbed into its circulation. Lower protein binding of drugs in the fetal blood as compared to that of the mother, results in higher concentrations of free (unbound) drug in the fetus for a given concentration of total drug. It is the free drug that enters the 'effect compartment' and exerts the pharmacological effect.

In general, although fetal drug metabolism can be detected in the embryonic phase, the fetal liver has limited capacity to metabolise drugs as a means of terminating their pharmacological action. There is experimental evidence for the presence of a variety of cytochrome P450 (CYP) enzymes in the fetal liver, including CYP1A1, CYP1B1, CYP2C8, CYP2D6, CYP3A4 and CYP3A5, to mention a few.[57] There are wide ontogenic changes in the predominance of metabolising enzymes in the fetus. For example, fetal CYP3A7 is the predominant CYP enzyme and its expression is decreases dramatically after birth, whereas in adults, CYP3A4 is the major functional enzyme of this subfamily.[58] At the present time, little is known about the clinical implications of these enzyme activities in the fetus as related to drug exposure. However, one has to bear in mind that several human teratogens are substrates for CYP enzymes, including ethanol, phenytoin and thalidomide. In a similar manner, drugs used in fetal therapy, such as phenobarbital and corticosteroids, are metabolised by these enzymes. Physiologically, 30% of the fetal hepatic blood flow is shunted through the ductus venosus at 20 weeks of gestation and 18% at 31 weeks of gestation, hence decreasing hepatic capacity to metabolise xenobiotics.

The persistence of a drug in the fetal compartment is determined by its rate of transfer from the fetus back to the mother, the distribution of the drug in the fetus and hepatic drug metabolism (table II). Pregnancy is characterised by physiological changes in the mother which may affect drug transfer to the fetus (table III and figure 1). The volume of distribution of most drugs increases during gestation as a result of increased maternal blood volume, body mass and fat content, as well as decreased drug protein binding[59] (table II). In addition, drugs are distributed into the amniotic fluid and often achieve concentrations higher than those achieved in maternal and fetal plasma. In parallel, there is an increase in the clearance rates of many drugs due to either enhanced rate of intrinsic hepatic metabolism, liver blood flow or renal elimination. For a minority of drugs (e.g. theophylline, caffeine) there is evidence of slower metabolic rate in pregnancy. Typically, both peak and steady state serum concentrations of drugs tend to be lower in

pregnancy. Because most fetal therapy regimens use the mother as the conduit for drug delivery, the pharmacokinetics of drugs in the mother will affect the rate and extent of fetal drug exposure. Only in a relatively limited number of instances, drugs have been injected directly into the fetal compartment to achieve a faster response or to elicit a response when maternal administration has failed (e.g. antiarrhythmics). Blood products (erythrocytes or platelets) which cannot permeate the intact placenta are always administered directly to the fetus. Despite the dramatic changes in fetal physiology and body composition throughout gestation, very little is known regarding the effects of these changes on fetal drug distribution and effects.

3. Ethical Considerations

Current research suggests that when a medication is clinically important for maternal well being, and even when safety has been shown for the fetus, many women refrain from therapy 'to be on the safe side'. Common conditions that exemplify this situation are nausea and vomiting of pregnancy, and asthma.[60,61] In contrast, when the fetus itself needs therapy, the majority of women will likely agree to endure risks which will prevent fetal morbidity, long-term sequelae or even death. It is essential for clinicians and researchers to ensure that these natural feelings are not exploited in recruiting patients to experimental protocols. The hopes given to the family must be realistic, including those relating to the potential benefits and risks of the drug to both fetus and mother and the risks/benefits of alternative therapies, if they exist.

The quality of evidence regarding efficacy and safety varies widely (table I), and communicating evidence to the family may be a difficult challenge for the healthcare team. Table IV proposes a paradigm of key questions that should be considered by the medical team and family when fetal drug therapy is contemplated. These should include comparison of both maternal and fetal risks of the therapy in question with those of other existing therapy. Last, the natural course of the untreated condition is critical, as it gives a context against which the risk of the therapy in question is weighted.

Information pertaining to fetal risk-benefit may change, as in the case of HIV, where the fetal safety of zidovudine has been established[62] but this knowledge is presently insufficient because of the combination of this drug with newer agents of undocumented fetal safety. The ethics of continuing placebo trials after a drug has been shown to be superior to placebo was the focus of debate following publication of the pivotal study showing the effectiveness of zidovudine over placebo in preventing fetal infection.[63] It is generally agreed that once evidence of superiority of a drug over placebo has been documented, the equipoise principle underlying the use of placebo does not hold any more.[64] In other cases, initially promising regimens have been proven to be of questionable value, as in the case of phenobarbital for the prevention of intraventricular haemorrhage.

The emergence of therapies for fetal arrhythmias reflects the difficulties in forming generalisable knowledge based on case reports or case series. As acknowledged by the authors of the largest

Table IV. The fetal pharmacotherapy ethical checklist

Healthy mother – sick fetus (e.g. adrenal cortical hyperplasia)	Sick mother – sick baby (e.g. HIV)
Does the drug have maternal risks? (e.g. Cushing's syndrome)	Does the untreated maternal condition bear maternal/fetal risks? (e.g. increased fetal morbidity with HIV)
What is rate and extent of risk?	What is the rate and extent of the risk?
Does the drug have fetal risks (e.g. neurobehavioral effects)?	Does pregnancy itself increase the risk of disease progression?
What is the rate and extent of the risk?	Does the drug have fetal risks?
Is there an alternative therapy?	Is there an alternative therapy? (e.g. combined antiretrovirals *vs* zidovudine)
Does it have a better risk-benefit ratio?	Does it have a better risk-benefit ratio?

existing series,[2] only a controlled, multicentre trial will be able to answer which drugs are more effective for specific arrhythmias. Here, the option of placebo is probably not viable because of the perception that the prognosis of many untreated arrhythmias is unfavourable. However, a controlled trial of treatment of fetal arrhythmias may compare two or more therapies believed to be effective.

Because of the uncontrolled manner in which data on fetal therapy have often been collected, the medical community often felt that it was too late to conduct randomised, placebo-controlled trials. In the case of antimicrobial therapy for toxoplasmosis, where no RCTs have ever been reported, it is unlikely that research ethics committees will approve the randomisation of infected mothers to placebo, thus leaving major questions on efficacy unanswered.

Yet, important data on efficacy have been collected for other infections (e.g. Group B streptococcus or HIV) by comparing the fetal outcomes of women who received antimicrobial therapy to those in whom such treatments were not given (e.g. lack of access to antiretroviral drugs in third world countries).

4. Therapies to Accelerate Maturation in the Prevention of Preterm Delivery

Several methods have been attempted over the years to accelerate fetal maturation in cases of imminent preterm delivery. This section focuses on the most widely studied regimen with corticosteroids.

4.1 Antenatal Corticosteroids and Neonatal Outcome

The maturational effects of corticosteroids on the fetus were first described in 1969.[65] Effects on fetal lungs include increases in surfactant production, expression of antioxidant enzymes and morphological maturation. In animals, corticosteroids induce myelination and functional maturation of the central nervous system[66] and decrease in blood-brain barrier permeability, thus possibly providing protection against intraventricular haemorrhage.[67] Enhanced maturation of the heart, kidney and gastrointestinal tract has also been demonstrated.[66]

The first RCT using antenatal treatment with betamethasone showed a significant reduction in the rates of mortality and of respiratory distress syndrome (RDS) in preterm infants below 32 weeks of gestation.[21] Numerous RCTs have corroborated these findings. A recent meta-analysis,[26] synthesising the results of 18 RCTs with over 3700 patients, showed decreased rates of RDS when delivery occurred 24 hours to 7 days after administration of corticosteroids [odds ratio (OR), 0.53; 95% confidence interval (CI), 0.44 to 0.63]. Associated protective effects included decreases in rates of mortality (OR, 0.60; 95% CI, 0.48 to 0.75) and of intraventricular haemorrhage [IVH] (OR, 0.48; 95% CI. 0.32 to 0.72). A similar trend was shown when corticosteroids were given less than 24 hours before delivery and for infants delivered more than 7 days after administration. No significant effect on the rate of necrotising enterocolitis was documented. However, this meta-analysis was criticised for ascertainment bias in some of the included studies.[68]

In cohort studies, antenatal corticosteroid use was associated with reduced incidence and severity of retinopathy of prematurity.[69,70] Recently, an association between antenatal betamethasone use and decreased rates of periventricular leukomalacia was observed.[71] Long-term follow-up of such patients have not shown any adverse neurodevelopmental effects.[72-74] Cohort studies have associated single doses of antenatal corticosteroids with increased rates of neonatal infections [relative risk (RR), 1.44, 95% CI 1.17 to 1.76] and necrotising enterocolitis (RR, 1.98, 95% CI 1.45 to 2.71).[27,28]

The significant healthcare implications of antenatal corticosteroid therapy resulted in recommendations for routine use at gestational ages of 24 to 34 weeks, when preterm delivery is anticipated.[75] Since the US National Institutes of Health (NIH) consensus conference in 1994, there has been a dramatic increase in the use of antenatal corticoste-

roids.[27-29] Whether this has resulted in the expected decrease in the incidence of RDS is less certain. Presently, several unresolved issues need to be addressed regarding antenatal corticosteroid use:

- As corticosteroids increase surfactant production, do they have any additive effects to those of postnatal surfactant administration? Meta-analysis of the three trials performed during the surfactant era[22-24] fails to show a significant reduction in rates of RDS (RR, 0.81, 95% CI 0.59 to 1.11).
- The evidence for the effectiveness of antenatal corticosteroids in reducing the incidence of IVH is based mainly on cohort studies. In these studies, women who received corticosteroids were likely to differ in their baseline characteristics from those who did not. In one study, the most important factors predicting corticosteroid administration were the hospital of admission and the length of hospital stay,[76] allowing for a number of co-interventions and fetal surveillance that may reduce the risk of IVH regardless of treatment with corticosteroids.
- Should corticosteroids be used in preterm premature rupture of membranes (PPROM), when delivery of an extremely low birth weight infant (less than 1000g) is expected or when there is multiple gestation? Meta-analysis indicates that the advantages of antenatal corticosteroids in the presence of PPROM remain uncertain,[77] but large prospective cohort studies do show decreased rates of RDS when pregnancy was complicated by PPROM, without increasing the risk of infection.[27,28] A recent RCT and a prospective observational study both failed to show significant benefits in infants weighing <1000g, or born earlier than 30 weeks gestation.[24,25] Although these findings need to be confirmed, a plausible explanation is that a certain degree of maturity is needed for corticosteroids to be effective. In multiple gestations, antenatal corticosteroids appear to be less effective.[78]
- Which corticosteroid should be used? The two corticosteroids routinely employed are betamethasone and dexamethasone, and it was largely believed that they are biologically similar. However, recently betamethasone use has been associated with a protective effect against periventricular leukomalacia (adjusted OR, 0.5, 95% CI, 0.2 to 0.9), an effect not exhibited by dexamethasone.[71] This could be related to other confounders, such as doctors' choice of one corticosteroid over another, and needs to be confirmed by further studies.
- Although it has become common practice to administer several courses of corticosteroids to women who continue to be at risk for preterm delivery,[79] presently, there is not enough evidence to evaluate their repeated use in women who remain undelivered.[26] On the basis of animal data, there are concerns regarding adverse effects on brain development after repeated doses of corticosteroids.[80] In humans, short-term post-natal corticosteroid treatment has been associated with diminished weight gain, head growth and increased incidence of neuromotor dysfunction.[81,82] In cohort studies, the number of repeated antenatal corticosteroid courses was inversely related to head circumference, birth weight and behavioural problems at 3 years of age.[30] Currently ongoing or planned studies should identify the potential advantages and adverse effects of repeated courses of antenatal corticosteroids.

5. Preventative Therapy

5.1 Prevention of Intraventricular Haemorrhage

A number of modalities have been studied over the years to try to prevent fetal morbidity that commonly leads to fetal death or to serious long-term sequelae in the child.

IVH is one of the most common causes of brain injury among preterm infants. Because IVH occurs most frequently during the first day of life,[83] effective intervention would need to take place antenatally or shortly after delivery. The proposed protective effect of phenobarbital against IVH is

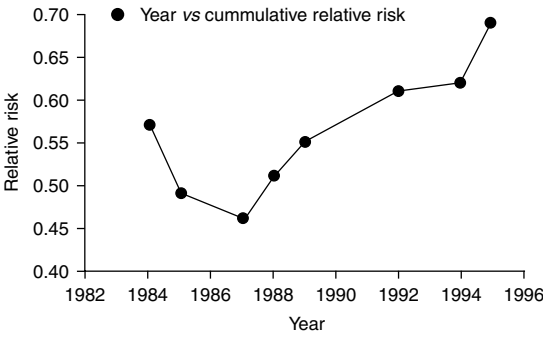

Fig. 2. Cumulative chronological meta-analysis of risk of intraventricular haemorrhage (IVH) with antenatal use of phenobarbital for the prevention of IVH. These data are taken from all available randomised, controlled trials.

on the basis of its ability to decrease both cerebral metabolic rate and to attenuate blood pressure changes.[84]

Reduction in the rate of IVH associated with phenobarbital was first demonstrated in 1981,[85] followed by at least seven additional trials.[31-37] In all the trials performed in the 1980's, antenatal phenobarbital treatment was shown to be beneficial in the prevention of either severe grades or all grades of IVH.[31-35] The evidence appeared compelling to the degree that it was considered to be the standard of care in many institutions.[86] However, the latest large RCTs failed to corroborate these findings.[36,37] A recent meta-analysis continued to show a protective effect of phenobarbital, although there was heterogeneity in the results.[38] When the studies are reviewed chronologically, there is an apparent trend towards a decreasing effect size of phenobarbital (figure 2). When assessed for possible confounders, the most likely candidate appears to be the concurrent antenatal use of corticosteroids, which has increased over the last decade. In some quasi randomised studies performed in the 1980's, corticosteroid use tended to be more prevalent in the treatment (phenobarbital) group. It appears that the effect size of phenobarbital in reducing IVH is directly related to the proportion of fetuses who received corticosteroids concomitantly (figure 3). Meta-analyses of the clinical trials that were not confounded by antenatal corticosteroid use[35-37] show no effect of antenatal phenobarbital use in preventing IVH (RR, 0.89; 95% CI 0.74 to 1.06). Thus, the evidence to date suggests that antenatal administration of phenobarbital does not exert an independent or synergistic effect to corticosteroids.

Long-term studies of young men exposed to phenobarbital antenatally documented a significant negative effect on verbal intelligence. Exposure that included the last trimester of pregnancy was the most detrimental.[18] *In summary*, the experience with phenobarbital in the prevention of IVH highlights the risks of drawing premature conclusions from methodologically suboptimal studies.

5.2 Prevention of Neural Tube Defects

Neural tube defects (NTD) occur very early in pregnancy and by 27 days post fertilisation, when many women are not even aware they have conceived, the closure of the neuropore is completed. The rates of NTD vary substantially, from 0.6 per 1000 live births in some parts of the US, to 12 per 1000 in coal mining valleys of South Wales. Most children with NTD have substantially reduced

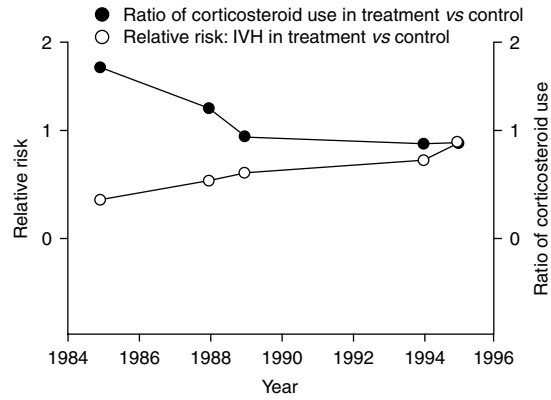

Fig. 3. The effect of antenatal phenobarbital administration on the occurrence of intraventricular haemorrhages [IVH] (expressed as relative risk) in parallel to the ratio of corticosteroid use in the treatment versus control groups. Data taken from all available randomised, controlled trials.

physical, neurological and intellectual functions. Early observations concluded that mothers of children with NTD had lower periconceptional intakes of vitamins in general and, specifically of folic acid. However, observational studies cannot prove causation, as other factors may be uncontrolled. Two randomised, placebo-controlled trials for primary prevention of NTD (with 400 μg/day folic acid) or prevention of recurrences (with 4mg of folic acid) documented the ability to prevent these debilitating malformations in a majority of individuals.[87,88] Characteristically, a woman's dietary intake of folic acid does not exceed 200 μg/day; hence, major changes would have to take place in the way folic acid is supplemented for a global prevention of NTD to be effective.

Although counselling can lead to appropriate folic acid supplementation,[89] such a strategy is not likely to affect the 50% of pregnancies that are unplanned.[86] Moreover, many physicians and pharmacists are still not routinely recommending the use of folic acid.[90] A public health campaign, conducted in China in areas of high and low rates of NTD, to use 400μg of folic acid daily starting from premarital examination has resulted in a decrease from 4.0 to 1.0 NTD per 1000 pregnancies in the high risk area and from 1.0 to 0.6 in the low risk area.[91] In 1996, the US Food and Drug Administration initiated folic acid fortification of flour with 140μg/100g, and the process was essentially completed in the US by mid-1997. As a result, mean folate levels in the population increased 2-fold to concentrations consistent with substantial decrease in the risk of NTD[92,93] (figure 4). However, even to date, when mean folate levels among women have been doubled, large numbers of women still have an increased risk for NTD and will, therefore, need to supplement with folic acid.

The prevention of serious fetal malformations by supplementing adequate amounts of an essential micronutrient, highlights the tremendous potential of well-designed research when followed by adequate public health implementation.

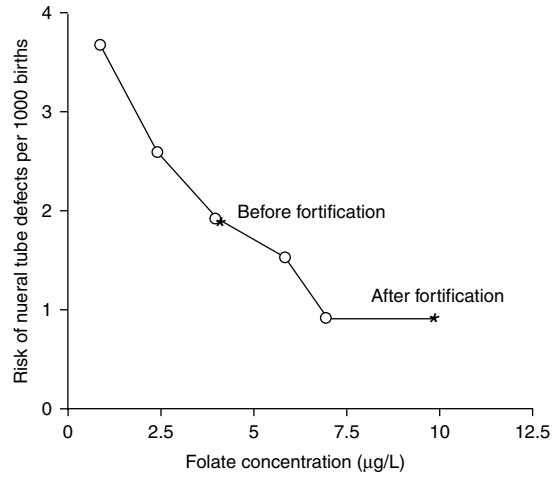

Fig. 4. Dose-response curve for folic acid and neural tube deficits. The asterisk denotes the risk in the US before and after implementing the folic acid fortification program, plotted on the dose-response curve.

5.3 Prevention and Treatment of Fetal Toxoplasmosis

The incidence of maternal toxoplasmosis during pregnancy has been estimated at 3 to 6 per 1000 live births in 'high risk' countries (e.g. France) or as low as 1 per 1000 live birth in 'low risk' countries (e.g. the US). Because most cases of maternal infection are asymptomatic, evidence of seroconversion or an increase in titres is needed to establish maternal infection. Examining fetal blood or amniotic fluid for fetal antibodies, parasite cultures or polymerase chain reaction (PCR) assays allows detection of fetal infection in various proportions of individuals.

The risk of fetal infection after primary maternal infection increases from 25% in the first trimester to 65% in the third trimester. Conversely, the risk for severe fetal sequelae is 75% in the first trimester, during embryogenesis, and decreases to practically none after 26 weeks of gestation. The serious adverse neonatal outcome of toxoplasmosis, including chorioretinitis, neuro-developmental delay and hearing loss, has driven immense efforts

Table V. Potential teratogenic and feto-toxic effects of drugs used in fetal therapy. Based on findings documented in humans

Drug	Potential effects
Corticosteroids	Increased risk of oral cleft in first trimester exposure[97]
	Adverse dose-dependent effect on birth weight, head circumference and behavioural development[30]
Phenobarbital	Potential adverse effects on cognitive development[18]
Indomethacin	Fetal closure of ductus arteriosus[98]
	Fetal/neonatal renal insufficiency
Zidovudine	Neonatal lactic acidosis, leukopenia,[99] thrombocytopenia
Amiodarone	Changes in fetal thyroid function[100]

towards education and primary prevention of toxoplasmosis.[94,95]

The mainstay of secondary prevention is the early use of the macrolide antibiotic spiramycin which is accumulated in the placenta to levels up to 5-fold higher than in maternal blood,[95] thus eradicating placental infection. Pyrimethamine and sulfadiazine confer an antiparasitic effect by inhibiting the parasite's folate synthesis. In animal species pyrimethamine has been shown to be teratogenic; the reported hydrops fetalis, cranial bone defects and brain anomalies seen in animals after large doses (12 mg/kg)[96] were not documented in clinical experience, with typical daily doses of only 0.5 to 1 mg/kg (table V). In this case, over-interpretation of the animal studies would have led to a potential loss of an important antiparasitic agent.

The assessment of effectiveness of antiparasitic therapy for gestational toxoplasmosis has been grossly hampered by the fact that none of the available studies was randomised or controlled. In cohort studies, women treated with spiramycin had significantly less risk of fetal infections than those not treated.[96] However, both groups tended to have similar proportions of the congenital syndrome, suggesting that spiramycin exerts much of its effect on the placental infection but is not capable of eradicating an already existing fetal infection. Although repeated reports confirmed a reduced risk of fetal infection and sequelae, in the existing studies untreated women tended to have infections later in pregnancy when compared with treated women, explaining higher rates of infection in them, and potentially lower rates of fetal sequelae. Another form of potential selection bias was due to the fact that programmes identifying fetal infection often initiated abortions of fetuses with detectable injuries, thus artificially improving the statistics of response to therapy.

A recent observational cohort study attempted to overcome the lack of RCTs by recruiting women in five reference centres.[50] The overall transmission of infection to the fetus was predicted only by the gestational age at which the infection had occurred and not by antimicrobial treatment. In contrast, when fetal infection occurred, administration of antimicrobial therapy conferred a protective effect against sequelae in general (OR 0.3, 95% CI 0.1 to 0.86), and severe sequelae in particular (OR 0.14, 95% CI 0.04 to 0.58). The sooner antimicrobials were given after the infection, the less frequently sequelae were seen.

Toxoplasma infections in pregnancy introduce difficult challenges in diagnosis and treatment. The reality created by the lack of any RCTs should be considered when future therapies are proposed for serious fetal infections.

5.4 Prevention of Fetal HIV Infection

In 1998, 1.2 million women and 590 000 children under 15 years of age were newly infected with HIV, mostly through their mothers before or during birth, or through breastfeeding. The rate of vertical maternal transmission in the absence of a therapeutic intervention ranges between 15 and 40%. Twenty five to 50% of all children with perinatally acquired infection develop AIDS within their first year of life, and 80% proceed to develop AIDS within 3 to 5 years. In 1998, 900 000 women and 510 000 children comprised more than half of all AIDS fatalities.

A pivotal RCT published in 1994 demonstrated the effectiveness of zidovudine during pregnancy and labour in reducing vertical transmission of

HIV from 25.5 to 8.3%.[12] Subsequent studies confirmed these results, showing the effectiveness of zidovudine even in mothers with advanced AIDS, or when administration started in late pregnancy.[101] Success rates were inversely related to maternal viral load, CD4+ cell numbers, length of prolonged rupture of membranes and preterm birth, and positively related to the rates of elective Caesarean section.[14,102] When preconception CD4+ counts were corrected for, there was no evidence of acceleration of disease progression during pregnancy.[103]

The long-term effects of *in utero* exposure to zidovudine among uninfected children born to HIV-infected women have been investigated among 234 such children. With a median follow-up of 4.2 years, there were no significant differences between zidovudine and uninfected placebo-exposed children in physical growth, laboratory values of markers of immune function, cognitive and developmental function, occurrence of neoplasms and rates of mortality.[96] Another study has partially confirmed these results but did not include behavioural tests as part of examining cognitive and developmental function.[104] These data contradict several animal studies, which reported adverse physical or neurobehavioural effects following much larger doses per kg of zidovudine[99,105] (table V). In contrast, studies in primates with doses resulting in plasma concentrations similar to those achieved in humans receiving 500 to 600 mg/day of zidovudine, showed no irreversible fetal effects. Similarly to in humans, mild anaemia, growth deficits and decreases in neonatal reflexes and abilities, which resolved gradually, were seen.

Although no RCTs have compared combined therapies to monotherapy with zidovudine, preliminary cohort studies have recently documented a nearly complete prevention of fetal infection with several combined therapies which included protease inhibitors.[15] Hence, the main issues today in secondary prevention of perinatal transmission of HIV are not necessarily the efficacy of existing therapies, but rather the access to and compliance with diagnostic tests and existing drugs.

Group B streptococcus (GBS) is the most common cause of neonatal sepsis in North America and a leading cause of neonatal mortality. Determinants associated with high risk for neonatal transmission of GBS include preterm delivery (<37 weeks gestation), rupture of membrane (>12 hours), known carrier state of GBS, temperature higher or equal to 100°F (38°C) fetal growth restriction, multiple gestation or a previous newborn infected by GBS. Protocols incorporating treatment of high risk women during delivery with penicillin and screening of low risk patients by means of rapid immunoassays or PCR assays, appear to reduce substantially the risk for neonatal infection.[106]

A recent meta-analysis of five trials revealed an 83% reduction in the risk of early neonatal infection (95% CI 61 to 93%) and a mean of 90% reduction in colonisation (95% CI 86 to 93).[107] Penicillin is the antibiotic of choice for GBS and it crosses the placenta readily.[108] In patients allergic to penicillin, clindamycin and erythromycin are commonly used. However, emerging GBS resistance to these agents may limit their future use. It has been estimated that the incidence of early-onset neonatal infections decreased by 65%, from 1.7 per 1000 live birth in 1993 to 0.6 in 1998, following the introduction of intrapartum antibiotic prophylaxis.[109]

6. Therapy for Fetal Disease

Table I lists a large number of modalities attempted over the years to treat fetal disease. Most of these therapeutic agents are administered to the mother, while in a minority of situations (e.g. fetal anaemia) directly into the fetal compartment. In the following section, we discuss one of the most widely treated groups of fetal pathologies.

6.1 Fetal Arrhythmias

Fetal arrhythmias are serious, life threatening conditions especially when they lead to hydrops fetalis. The goal of therapy is to reach an adequate ventricular rate and optimal conversion to sinus rhythm.

Table VI. Case series of fetal pharmacotherapy for arrhythmias

Reference	Type of fetal arrhythmia	No.	Mean/median age at detection	Successful response to maternal digoxin monotherapy	Response to other drugs
Jaeggi et al.[110]	Atrial flutter	15	34 (mean)	5/11	
Simpson et al.[2]	SVT/Atrial flutter	105/22	32 (median)	62% of non-hydropic	In hydropic fetuses: 1/5 with digoxin and 8/14 with digoxin + verapamil; 16/27 with flecainide
	hydropic	52			
	non hydropic	75			
Lisowski et al.[111]	Atrial flutter				
	hydropic	17		8/9	Sotalol 0/1; digoxin plus 4/7 = procainamide/quinidine, flecanide, propaphenone, sotalol (1 received umbilical vein digixon plus sotalol)
	non hydropic	18		15	Sotalol 7/8; digixon + sotalol 5/5

SVT = supraventricular tachycardia.

Treatment of life threatening fetal arrhythmias is a powerful example of the fetus being a target for drug therapy. Most anti-arrhythmic drugs used in adults and children have been tested for fetal arrhythmias (table I), yet there is not even a single controlled study in this area (table VI). Digoxin has been by far the most commonly used drug with an estimated 50% success rate for supraventricular tachycardia and atrial fibrillation. In addition to treating the arrhythmia, its inotropic properties help counteract the hydrops. The existence of atrial fibrillation and hydrops fetalis predicts poor outcome. In different series, sotalol and flecainide appear to be equally effective (table VI). The efficacy of other agents is more difficult to evaluate, especially in view of the fact that they are often being given as a second line option.

As concluded by the authors of the largest published series of 127 cases, 'there is no ideal treatment protocol for these fetuses and a large prospective multicentre trial is required to optimise treatment of both hydropic and non-hydropic fetuses'.[2]

7. Conclusion

The relatively short history of fetal pharmacotherapy highlights several critical issues that need to be addressed in the future. Often, new modalities entered practice without evidence-based proof of effectiveness. Once anecdotal reports or case series have been accumulated, it becomes difficult to perform controlled studies because of the misperception of an ethical dilemma in not treating with an available drug (e.g. toxoplasmosis). In the case of folic acid for the prevention of NTD, after case-control and partially controlled intervention studies, there was a wide perception in North America that it might be unethical to withhold folic acid from women in the context of randomised, placebo-controlled studies. Yet, without the two RCTs that were conducted in Europe, would the FDA have the scientific rigour needed to execute its folate fortification program?

The rise and fall of phenobarbital as a remedy for IVH prevention highlights the reality that RCTs by themselves do not guarantee scientifically correct answers, if these trials are not well designed to avoid bias.

It is conceivable that scores of new modalities of fetal therapy will be introduced in the next few years. These may include emerging therapies such as stem cell therapy or fetal pain management. The ethical imperative should always include optimally informed parents, in terms of short- and long-term risks and benefits of the experimental modality, its alternatives, and the risks of not intervening.

The clinical imperative must acknowledge that for rare fetal conditions, RCTs are difficult to perform and will need multicenter participation (e.g. for fetal arrhythmias). Other experimental designs, such as rigourously collected cohorts, or n = 1 stud-

ies, should also be considered when conditions do not allow multicenter RCTs. Without rigorous design and execution, medicine will not be able to address optimally the needs of the most vulnerable of all patients, the fetus.

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