DRUG HAZARDS TO THE HUMAN EMBRYO, FOETUS AND NEWBORN INFANT—A REVIEW*

by

H. C. Agarwal, M.D., D.C.H.

D. P. Mukerjee, M.D., D.C.H.

and

Dinesh Mohan, M.D., D.C.H.

Recently, evidences have sounded on the hazards of drugs after the discovery of unpredicted foetal anomalies resulting from prenatal ingestion of the drug Thalidomide and Rubella infection. The accumulated clinical experience indicates that drugs and infections pose two major threats to the successful outcome of pregnancy and for the neonate's adjustment and survival. In the last decade, the noxious influences of drugs to the embryo, foetus or neonate have been increasingly recognised and reported on all over the world. The present paper reviews briefly the current knowledge of suspected or established drug effects with an aim to provide:

(i) A firm basis to the obstetrician for weighing the foetal risk and maternal benefit of any contemplated therapy.

(ii) An aquaintence to the paediatrician for identification and management of some curiously unexpected symptoms and signs, and

(iii) A guidance to both of them for making some beneficial observations in future and describing many foetal drug effects which are unknown as yet.

Evaluation of drug hazards

A sound basis for the critical evaluation of the hazards of drugs upon the developing embryo or foetus when given to pregnant women, or of the adverse effects from direct administration to the newborn infant, especially the premature one, has not yet been established. Trial of drugs on animals does not ensure safety because of the species differences in the response of drugs, e.g., thalidomide has no teratogenic potential for certain animals though it certainly has for human embryos, while salicylates are more teratogenic for certain animals than for human beings. Any drug harmful to the mother may naturally be dangerous to the foetus. But certain drugs like thalidomide, which are harmless to pregnant woman, may also produce adverse effects on the foetus. Further, the harmful effects on the foetus depend upon the basic structure of the drug, the dosage and the duration they have been given. The type of ill-effects depends on the stage of pregnancy at which the drugs are given to the mother, the critical periods being

*From S. N. Medical College, Agra.

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either first 12 weeks or the last week of pregnancy and labour.

Types of drug hazards

The adverse effects of drugs on the foetus and the newborn when administered during pregnancy or labour or directly to the newborn are enumerated in Table I.

TABLE I

Summarising the drug effects on the embryo, foetus and newborn infants

Drugs	Abnormalities
I. DRUGS AFFECTING CENTRAL NERVOUS SYSTEM:	
(i) Thalidomide	Phocomelia, foetal death, hearing loss, multiple congenital malformations.
(ii) Barbiturates (excessive amounts)	Neonatal bleeding, drowsiness and difficult feeding.
(iii) Morphine and Heroin	Respiratory depression, slow to breath, convulsions, neonatal death.
(iv) Anaesthesia (prolonged)	Foetal maladjustment, pulmonary hyaline membrane disease (?)
(v) Salicylates (large amounts)	Neonatal bleeding, foetal damage and miscarriage.
(vi) Phenothiazines and Chlorpromazine	Hyperbilirubinemia (?)
(vii) Meprobromate	Retarded foetal development (?)
(viii) Meclizine	Congenital malformations.
II. DRUGS AFFECTING CARDIO-VASCULAR SYSTEM:	
(i) Reserpine (Serpasil)	Nasal congestion, respiratory distress and drowsiness.
(ii) Hexamethonium bromide	Paralytic ileus in premature infants
(iii) I. V. fluids (excessive amounts)	Fluid and electrolyte imbalance
(iv) Cardiac glycosides	Effect on foetal heart (?)
(v) Adrenaline & Noradrenaline	Foetal asphyxia from constriction of uterine vessels (?)
(vi) Anticoagulants	Haemorrhage and foetal death
(vii) Ammonium Chloride	Acidosis
III. HORMONES AND ANTITHYROID DRUGS:	
(i) Oral progestins, testosterone, androgens and oestrogens	Masculinization of female foetus, Advanced bone age
(ii) Corticosteroid and ACTH	Cleft palate
(iii) Thiouracil, Lugol's Iodine & Radio active Iodine^{131}	Nontoxic goitre and hypothyroidism
(iv) Teridex, and Iodine containing dyes	Elevation of serum protein bound Iodine
(v) Phenmetrazine (Preludin)	Diaphragmatic hernia
(vi) Oral hypoglycemics -Sulphonyl urea derivatives -Phenfermin (D.B.I.)	Multiple congenital anomalies (?) and abortions Iactic acidosis
(vii) Insulin shock	Foetal shock

Drugs	Abnormalities
IV. ANTIBIOTIC AGENTS:	
(i) Tetracyclines	Inhibition of skeletal growth, abnormalities and late eruption of teeth
(ii) Chloramphenicol	Cardio-vascuar collapse, Gray syndrome, Hepatic toxicity
(iii) Novobiocin	Hyperbilirubinemia (hepatotoxic)
(iv) Erythromycin	Liver damage (?)
(v) Neomycin, Polymyxin, Vancomycin	Nephrotoxic and ototoxic
(vi) Streptomycin	Ototoxic
V. ANTIMETABOLITES:	
(i) Aminopterin, Amethopterin and Chlorambucin	Congenital malformations, retardation of foetal growth
(ii) 6-mercaptopurin, Myeleran and Nitrogen Mustard	Foetal anomalies (?)
VI. OTHER CHEMOTHERAPEUTIC AGENTS:	
(i) Sulphonamides (Gantrisin, madribon)	Kernicterus (Hepatic toxicity)
(ii) Nitrofurantin	Haemolysis - hyperbilirubinemia
(iii) Quinine	Congenital malformations of ears and eyes, thrombocytopenia, ototoxic, foetal death
(iv) Chloroquine	C.N.S. damage, foetal death (?)
(v) Thiazides	Neonatal thrombocytopenia
(vi) Vitamin K Analogues	Hyperbilirubinemia (hepatotoxic)
(vii) Napthalene, Primaquine, Phenyl hydrazine	Haemolysis - hyperbilirubinemia
VII. MISCELLANEOUS AGENTS:	
(i) Carcinogenic agents (Benzanthracine, Methyl Cholanthrene)	Tumours and foetal death
(ii) Smoking	Premature birth, low birth weight
(iii) Vaccination	Foetal vaccinia
(iv) Poliovaccine (Live)	Foetal loss (?)
(v) Oxygen (in premature neonates)	Retrolental fibroplasia

Drug hazards may be of following 5 types:

A. Anatomic malformations.
B. Foetal death.
C. Defective foetal growth.
D. Interference with neonatal adjustment.
E. Miscellaneous toxic effects.

A. *Maternal drugs resulting in anatomic malformations*

The embryonic period (first trimester) is the period of differentiation and organogenesis. Environmental interference during this period may result in anatomic sequelae in the foetus. The noxious agents pro-

duce adverse effects on the organs only during the period of their rapid differentiation and not in the resting stages. The following are the potentially toxic drugs for the developing embryo.

1. *Thalidomide:* This drug, a non-barbiturate sedative, was marketed in 1960-61. In the ensuing year, a remarkable increase in phocomelia was correlated with the ingestion of the drug early in pregnancy by clinicians in Australia, England and Germany. Warkany and Kalter (1964) reviewed 4500 affected children and noticed 100% melformation rate when the drug was taken, even in small amounts, from 34 to 45 days after the last menstrual period. The spectrum of malformations included abnormalities which involved the extremities, the ears and auditory meatus, the eyes, the heart, the gastro-intestinal (atresia of oesophagus, duodenum and anus) and urogenital systems, capillary naevi and haemangiomas. The limb abnormalities are usually symmetrical and affect arms more than legs.

2. *Cancer chemotherapeutic agents:* Aminopterin (Amethopterin) is definitely teratogenic in human beings, while 6-mercaptopurines, myleran, urethane and nitrogen mustard, though associated with foetal anomalies, are not proven teratogenic. Sokol and Lessman (1960) observed that use of aminopterin in the first trimester lead to malformations like harelip, cleft palate, hydrocephalus, meningo-myelocele, ear and eye deformities or abortion in 22% infants.

The probable relation between the maternal chlorambucil and foetal abnormalities is reported by Shotton and Monie (1963) who found absence of kidneys and ureters in the foetus whose mother received this drug from 5th to 9th week after the last menstrual period. Possibly radiation like effects from some of these agents may increase genetic mutation rates or cause anomalies due to induced chromosomal abnormalities (due to nucleotoxic effects of these drugs on active cell division and metabolism of the foetus).

3. *Antimalarial drugs (i) Quinine:* Apart from its use as an antimalarial, quinine is also frequently used as abortifacient. Winckel (1948) reviewed 17 cases of congenital anomalies of the eye and ear due to quinine administration early in pregnancy. The damage to auditory apparatus depends on foetal sensitivity or excessive dosage of quinine.

(ii) *Chloroquine:* Its structure resembles quinine and is potentially teratogenic. Hart and Naunton (1964) have described the effect of chloroquine therapy in a woman with lupus erythematosus. During her 1st, 4th and 7th pregnancies, she received no chloroquine and delivered normal infants. In the 6th pregnancy, which terminated in an abortion at 12th week, she got chloroquine throughout. Her 2nd, 3rd and 5th pregnancies, in which she had chloroquine therapy, resulted in hemihypertrophy and Wilm's tumour in one, deafness with cochleo-vestibular paresis and mental retardation in other two.

4. *Androgenic steroids:* They are now frequently used as oral contraceptives. Wilkins (1960) observed masculinization of female foetuses whose mother received androgen in

the 1st trimester of pregnancy. These testosterone derivatives with progestational properties, unlike natural progesterone, are clearly androgenic to the foetus. Further, 17-α-ethinyl-19 nor testosterone (Norlutin) has been found 5 times as effective a female masculinizer as 17-α-ethinyl testosterone (Progestoral).

The clitoral hypertrophy due to these agents becomes non-progressive postnatally, in contrast to the progressive adrenocortical virilism. Talbot and Crawford (1964) have suggested that irrespective of the history of drug ingestion during pregnancy a urinary 17-ketosteroid estimation and buccal smear for sex identification should be done on 5th day. Should the former be more than 3 mg/day, the infant certainly has progressive adrenocortical virilism.

Bongiovanni *et al* (1959) had reported 4 cases of masculinized female infants with diethyl-stilboestrol therapy during pregnancy. This is probably due to stimulation of foetal adrenals by stilboestrol to increase the output of androgens.

5. *Corticosteroids:* A.C.T.H. and hydrocortisone have produced cleft palate in mice. Bongiovanni and McPadden (1960) observed 4 cases of cleft palate in 260 pregnancies in which corticosteroids were given in large doses before the 14th week.

6. *Tetracycline:* The teratogenic potential of tetracycline in human embryo is noted by Carter and Wilson (1962) who reported an infant with bilateral deformities of the hands whose mother had received the drug for 4 days early in the pregnancy. Some have also tried to correlate maternal ingestion of tetracyclines and unilateral or bilateral cataracts in infants, but this awaits further confirmation.

7. *Antidiabetic compounds:* A probable teratogenic action of sulphonylurea therapy was noted by Larrson and Sterky (1960) on a young diabetic woman treated with tolbutamide who delivered an infant with multiple congenital anomalies. Comparative trial of sulphonylurea derivatives on pregnant animals has revealed that carbutamide has got the highest, tolbutamide, in between and chlorpropamide, the lowest, teratogenic potency.

8. *Maclizine:* Patterson (1964) reported congenital malformations in 5.3% infants of mothers receiving Maclizine, the incidence being 12% during 5th to 6th week of pregnancy. But Warkany and Kalter (1964) found no congenital malformations with Maclizine in the doses used in pregnant women.

9. *Phenmetrazine (Preludin):* It is a drug for obesity in pregnancy but may be teratogenic to the human foetus. Powell and Johnstone (1962) have reported two infants with hu diaphragmatic hernias whose moth took Preludin in the 1st trimester her 1st and 3rd pregnancies.

10. *Vitamin D:* Garcia *et al* (1964) have recently described a syndrome of supravalvular aortic stenosis, mental subnormality, a peculiar facies and difuse osteosclerosis in neonates due to maternal ingestion of excess of vitamin D during pregnancy. But it would be premature to imply a causal relationship.

B. *Maternal drugs resulting in foetal death*

Drugs given to the mother, if severely noxious, may lead to foetal death at any time during gestation. Such are following drugs:

1. *Quinine:* Quinine is a well known abortificient, as it can cross the placental barrier. A few recorded cases of foetal death associated with maternal ingestion of quinine seem to give this drug a sinister obstetrical reputation.

2. *Cancer chemotherapeutic Agents:* Aminopterine, like quinine, is also an abortifacient (Parish, 1935). In some instances intrauterine death and abortions have been attributed to an antifolic acid compound.

3. *Anticoagulants:* Dicoumarol, used for thrombosis in pregnant women, results in foetal bleeding and death at a later stage of pregnancy (Gordan and Dean, 1955). However, heparin has been proved to be safe and effective and also does not cross the placenta, because of its molecular size.

4. *Antidiabetic compounds:* Diabetic mothers treated with insulin and other oral antidiabetics often have abortions and stillbirths. Jackson *et al* (1962) noted a high incidence of perinatal abnormalities (31%, 55% and 63%) with insulin, sulphonylurea and chlorpropamide respectively in a series of diabetic mothers.

5. *Carcinogenic agents:* Direct application of carcinogens like Benzanthracene, Benzpyrene and Methyl Cholanthrene have caused tumours in the transplanted embryonic tissue. Early injection of Dibenzanthracene into the amniotic fluid has resulted in foetal death.

6. *Live polio-vaccine:* Immunization of a non immune pregnant lady with live poliovirus (Sabin) may occasionally result in viraemia, and consequent exposure of the foetus to congenital anomalies or even destruction (Page, 1964).

7. *Narcotics:* Maternal narcotic withdrawal before delivery may result in an increase of foetal movements and occasionally foetal death.

8. *Salicylates:* Salicylates in large doses may lead to foetal damage. Jacksen (1948) recorded miscarriage in a patient who had attempted suicide by aspirin.

C. *Maternal drugs influencing foetal growth*

The period from 12th week to birth of intrauterine life is devoted chiefly to the growth of the foetus. Following drugs may influence the growth potential of the foetus temporarily or permanently:

1. *Cancer chemotherapeutic agents:* These drugs produce structural abnormalities and retard the growth of the foetus. Aminopterin infant reported by Warkany *et al* (1959) weighed 1280 gms at 42 weeks gestation. The busulfan infant reported by Diamond *et al* (1960) weighed 1077 gms at 39.5 weeks gestation.

2. *Cigarette:* The infants of cigarette smokers are born early and weigh less (Lowe, 1959), probably due to chronic hypoxia of the foetus. This recalls the reports of an increased foetal heart rate when a pregnant

woman begins to smoke. (Sontag and Wallace, 1935).

3. *Tetracycline*: In the last trimester of pregnancy it crosses the placenta rapidly, is widely deposited in the foetal skeleton and interferes with skeletal growth and eruption of teeth of the infant (Cohlan *et al* 1963).

4. *Maprobromate:* Some have attributed retardation of foetal development, but this awaits further proof and confirmation.

D. Maternal drugs interfering with neonatal adjustment

Following drugs, taken by the mother at any time up to delivery, may lead to imperfect neonatal adjustment:

1. *Antithyroid drugs:* Foetal thyroid is a functionally active gland. Maternal ingestion of thiouracil, radioactive iodine etc. may produce hypothyroidism and goitre in the newborn (Aaron *et al* 1955). The goitre may manifest as respiratory distress, cyanotic episodes, inability to feed and severe jaundice. Surprisingly, the hypothyroidism due to Iodine^{131} may be permanent.

Conally (1964) observed that certain iodine containing compounds like Lugol's solution, Biligraffin, Lipiodol etc. lead to elevation of serum protein bound iodine for one month to one year, and the neonate may develop symptoms like constipation and umbilical hernia, simulating congenital hypothyroidism. Recently it has been discovered that coating on PAS tablets contain iodine sufficient to elevate serum protein bound iodine.

2. *Narcotics:* Morphine or pethidine given to the mother within few hours of delivery may result in slow spontaneous breathing in the neonate, especially the premature. Cobrink *et al* (1955) have described a syndrome of neonates characterized by dyspnoea, cyanosis, vomiting, poor feeding and sweating due to maternal ingestion of morphine.

3. *Depressants:* Maternal barbiturate premedication could affect the baby's ability to establish adequate breast feeding up to 6 days (Strechler, 1964). The affected babies also become drowsy.

4. *Phenothiazine Derivatves:* Scokel and Jones (1962) detected a correlation between phenothiazine drugs (a sedative) in the mother and jaundice and haemorrhagic phenomena in the premature infant (but not in term infant), but subsequent studies did not confirm this finding.

5. *Anaesthesia:* During labour, anaesthesia should be given very carefully, for the incidence of foetal maladjustments and pulmonary hyaline membrane disease is higher in these children. The former is attributed to the anoxia which develops during the course of anaesthetic procedures.

6. *Reserpine:* Budnick *et al* (1955) observed that 16% infants born of 77 reserpine treated mothers had a snuffy nose with nasal discharge, costal retractions, cyanosis and anoxia which persisted for one or two days. Further, such infants may develop hypertonicity, decreased foetal activity and hypothermia even before the appearance of snuffy nose.

7. *Hexamethonium bromide:* It is a ganglionic blocking agent, also used

in toxaemia of pregnancy. Morris (1953) had reported 3 cases of paralytic ileus (2 died) out of 10 infants of mothers who received this drug.

8. *Fluid and electrolytes:* Battalgia *et al* (1960) infused pregnant women with 5% glucose (hypotonic) and 20% mannitol (hypertonic) solutions. The former resulted in cerebral oedema in the newborn due to diminished total osmotic pressure and hyponatremia. The latter increased foetal total osmotic pressure and decreased plasma protein concentration.

9. *Quinine:* Administration of quinine to the mother to induce labour had resulted in thrombocytopenia in both the mother and her infant (Posner, 1937). Quinine produces maternal thrombocytopenia by combining platelets and confering upon them the properties of a weak antigen. The neonatal thrombocytopenia, however, results from transplacental passage of both antibody and quinine.

10. *Thiazides:* Antepartum administration of thiazide drug leads to neonatal thrombocytopenia in 7 cases (Rodriguez *et al* 1964). The thrombocytopenia was due to ineffective bone marrow production of platelets, either due to isoimmunization or incompetent bone marrow.

11. *Vitamin K analogues:* Lucey and Dolan (1959) noticed that 6 of the 9 infants, whose mothers received 72 mgs. of Hykinon (synthetic vitamin K) during labour, required exchange transfusion for the ensuing jaundice and kernicterus. The jaundice results either from red cell breakdown due to some metabolic abnormality or inability of infant's liver to clear bilirubin, especially in prematures.

12. *Naphthalene:* Zinkham and Childs (1958) had reported haemolytic anaemia in neonate whose mother had ingested mothballs (Naphthalene) during pregnancy. The infant's susceptibility was due to deficient G-6-PD in R.B.C.S. — on enzyme which maintains glutathione in a reduced state and offers protection to R.B.C.S. Infants'red cells are also predisposed to destruction by primaquine, nitrofurantoin, phenylhydrazine etc.

13. *Sulphonamides:* Long acting sulphas like Madribon and Gantrisin administered to the mother persist much longer in the infants than in the mother, (Lucey and Driscoll, 1959). When given in large doses to the pregnant mother near term, they increase the neonate's susceptibility to kernicterus, probably due to their hepato-toxic effect which prevents conjugation of bilirubin, and by causing bilirubin-albumin dissociation in the blood.

14. *Chloramphenicol:* The reduced rate of conversion of free and potentially toxic chloramphenical to its glucuronide in the liver and of its slow renal excretion with consequent high blood levels of chloramphenicol may lead to Gray Syndrome (Nelson, 1964) in newborn infants, especially premature ones. On the 3rd or 4th day of therapy, regurgitation or vomiting of feeds, abdominal distension, respiratory distress, flaccidity and an ashen gray colour develops, which may be fatal within 24-48 hours. Sometimes, during chloramphenicol therapy, a competetive de-

fective conjugation of haemobilirubin (due to hepatic immaturity) may result in higher levels of indirect bilirubin in the blood which is neurotoxic.

E. *Maternal drugs producing miscelaneous toxic effects*

Administration of certain drugs to the mother or newborn may have remote and unclassified harmful effects on the foetus and neonate, which become obvious only as the child develops and deviates from normal. The followings are such potentially toxic drugs:

1. *Streptomycin:* It traverses the human placenta from the 2nd to the 9th month of pregnancy and is potentially toxic to the foetus (Watson and Stow, 1948), particularly when there is maternal kidney disease. Large doses of streptomycin have resulted in prolonged coma and even death in newborn infants.

2. *Tetracycline:* Wallman and Hilton (1962) have reported teeth abnormalities like yellow or brown pigmentation and enamel hypoplasia in 46 out of 50 tetracycline treated infants, which become obvious with the eruption of teeth which were developing during the period of drug administration. The severity of abnormality was proportional to the dose of tetracyclin and prematurity.

3. *Newer antibiotics:* Kennamycin, Vancomycin, Neomycin and Polymyxin should be used cautiously, or better avoided, in pregnant woman at term or in the newborn, as they are potentially nephrotoxic and ototoxic. Novobiocin has been shown to cause hyperbilirubinemia in newborn infants.

4. *Drugs toxicity due to newborn's enzymatic deffects:* The hepatic microsomal enzyme systems are defective, which are essential for the metabolism of aminopyrine, amphetamine, chlorpromazine, hexabarbital and phenacetin. Neonates also have low levels of pseudocholinesterase which may increase their susceptibility to the effects of succinyl choline used as an adjunct to anaesthesia (Nelson, 1964). The ability of term and premature newborn infants to acetylate compounds containing free amino or related groups is reduced, as shown by their limited capacity to acetylate sulphonamides.

5. Many drugs, e.g., barbitu[illegible], bromides, iodides, salicylates, opium, atropine, sulphonamides and cascara, are excreted in the breast milk and exert an effect on the foetus and neonate. Hence physician should be as sparing as possible in the administration of these drugs near term or to nursing mothers.

6. *Oxygen:* Prolonged and injudicious administration of high concentrations of oxygen to premature infants for the relief of respiratory distress and cyanosis, may lead to retrolental fibroplasia and consequent partial or complete blindness.

7. *Broad spectrum antibiotics in premature infants:* Broad spectrum antibiotics are not absorbed properly when administered either intramuscularly or orally (because of local tissue irritant reaction and relative circulatory inadequacy). Their injudicious administration may lead to dangers of:

(a) Superinfection with organisms resistant to antibiotics.

(b) Inhibition of intestinal bacteria which synthesize vitamin K and thiamine and
(c) Deliterious interference of some important metabolic processes of e.g., role of sulfisoxazole in hyperbilirubinemia.

Summary and Conclusion

The present knowledge of the unforeseen and undesired effects of the drugs on the developing embryo, foetus and newborn has been dramatically expanded since early 1960s. The spectrum of adverse influences has ranged from defective foetal growth, congenital malformations and foetal death to neonatal maladjustment and a host of other toxic effects.

The established relation between maternal drug and foetal disorder provides a judicious and timely warning with respect to their use in pregnant women; the severity and frequency of the foetal effects must be balanced against the risk of not giving the drug. Much more attention should be given to drugs of potential hazards especially the sedatives, antimetabolites, antimalarials, analgesics, antithyroids, anticoagulants, androgens and adrenal cortical hormones.

The use of drugs in the term and premature newborn infant should also be cautious and sparing, with the dosage adjusted downwards and the interval between doses lengthened to account for the renal, hepatic and enzymatic immaturity of the neonates. Drugs like chloramphenicol, newer antibiotics, long acting sulphonamides, analgesics, sedatives, primaquine, phenylhydrozine, vitamin K and other newer drugs should be administered to them only under controlled conditions. Their trial on older children and adults or on the basis of animal experimentation does not assure safety to the newborn.

Observing a multitude of noxious effects of inumerable drugs, Kalter and Warkany have rightly emphasized that at present, more children die from congenital malformations than from contagious dieases which were dangerous before the modern era of chemotherapy. The aquaintence of obstetrician and paediatrician of unusual foetal and neonatal responses with potentially toxic drugs should promptly lead to the most fruitful attack on such major current medical problems as congenital malformations, pregnancy wastage, neonatal death and neuromuscular handicaps of childhood and later years.

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