# THE BIOCHEMICAL EFFECTS OF DRUGS IN PREGNANCY

## VOLUME 2: DIURETICS, DIGESTIVE AND PULMONARY TRACT DRUGS, HORMONES, ANTIHORMONES AND STEROID HORMONES; ANALGESICS, METABOLIC ACTION DRUGS, ANTIBIOTICS AND CHEMOTHERAPEUTIC SUBSTANCES, VACCINES AND SERA

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# Preface

Society has always striven to protect the pregnant woman. In ancient Greece and pharaonic Egypt special attention was paid to the diet, hygiene, and drug treatment of the expectant mother. The dangers of certain drugs in pregnancy were mentioned by Mauriceau in the second half of the 17th century. At the end of the 18th century the concept of birth malformations being due to 'divine anger' began to be replaced by more biological explanations. In the middle of the 19th century Da Reste [1] and others began research on experimental teratogenesis, and it was shown that some foetal malformations could be caused by chemicals.

Ancel (1933) [2] showed that chemical or physical agents could have a reproducible teratogenic effect in mammals and birds if applied at particular stages of development. However, concern about teratogenicity in human pregnancy is quite recent. In 1959 such possibilities were discussed [3], but it was the thalidomide disaster of 1960 which brought the subject to everyone's attention. Since that time the use of drugs in pregnancy has become a highly emotional issue. A logical approach to the problems of drugs in pregnancy is to gather information on drug safety in a systematic way, assessing the risk to benefit ratio for all drugs likely to be used in pregnant women. This is a mammoth task, but the present work is an attempt to do this in a comprehensive way.

In recent years, work on the teratogenicity of drugs has noticeably increased, but so far as the practising doctor is concerned the literature is not helpful. Package inserts which state 'To be used with caution in pregnancy' do not contain enough specific information to be useful.

In publishing this book we hope to provide more precise, more useful and more complete data. We hope that clinicians will respond by contributing their own experiences or drawing our attention to literature we have overlooked. In this way future editions may, we hope, be improved.

A. ONNIS

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**PUBLISHERS' NOTE**

***Since the safety of drugs and their administration to both pregnant and non-pregnant patients is constantly under medical and scientific review, it is always wise to check the most recent literature when prescribing drugs discussed in this book. Drugs quoted in the text are not necessarily in line with normal therapeutic drug doses prescribed to patients, as in most cases drugs in this book were prescribed on a purely experimental basis.***

# Introduction

There is no doubt that over-prescribing of drugs is a major problem in modern medicine, and nowhere is unnecessary use of drugs more dangerous than in pregnancy. On the other hand, modern drugs have made a major contribution to human health, and even in pregnancy drugs still play an important part in treating maternal diseases and in relieving pain in labour.

In an ideal world no medical treatment would be required in pregnancy, but the reality is that many women develop conditions requiring treatment when they are pregnant. An absolute ban on drug usage in pregnancy would not be practical, and in any case would be as logical a response to the thalidomide disaster as abolishing air travel after a single aircraft crash.

Unfortunately, not all responses to disasters are logical, and in the case of drugs in pregnancy some of the responses are not medical. The issue has become one of public policy and legal responsibility, and it even has a political dimension.

In this complex situation the prescribing doctor finds himself in difficulty. He is perhaps not well read in the science of teratogenicity, but he knows that the patient is half informed about the risk of drugs in pregnancy and will blame any adverse event in the pregnancy on the drugs which he prescribes.

In such a situation the doctor should be able to talk knowledgeably to the patient of risks and benefits for the drug concerned. It has been our aim to supply the information he requires. The present book is certainly not infallible, and no doubt some recommendations will change in the future as a result of new information. It is, however, as complete as we are able to make it. If there are errors or omissions we would be grateful to hear of them.

## EFFECTS OF DRUGS ON THE FOETUS

The effects of drugs given to pregnant women, the embryo, or foetus are difficult to predict. A summary of the main considerations as to the effects of drugs on the products of conception will now be given, leaving a more detailed consideration for later [1, 2, 3, 4].

### Maternal pharmacokinetics and pharmacodynamics

Large physiological changes occur in pregnancy. Maternal weight increases not only because of growth of the products of conception and expansion of the uterus but because of an increase in circulating blood volume and body water. There is an increase in oxygen consumption, in basal metabolism, cardiac output, and red cell mass; and there are changes in the distribution of cardiac output, with particular increases in uterine and renal blood flow. The resistance and tone of blood vessels all over the body are changed. There is a profound change in renal physiology; an increase in glomerular filtration rate and alterations in tubular function. This is not all, for there is a change in the metabolism of protein, lipids, and carbohydrates, and changes in electrolyte balance. The alterations that occur in plasma proteins could and do have an important bearing on the distribution of drugs, many of which are highly protein bound.

The alterations in coagulation factors have an obvious significance for the requirement of anticoagulants. In women who develop complications of pregancy, such as diabetes, hypertension, and renal impairment, the situation is still more complicated.

### Transplacental passage of drugs

The placenta is still widely thought of as being a barrier between the mother and the foetus. For the majority of drugs this is an erroneous concept. It is also worth remembering that prior to the development of the placenta some drugs will be present in the tubular and uterine secretions and in contact with the blastocyst even as it migrates towards the point of implantation. The mechanisms which regulate the transfer of drugs from mother to foetus are the following:

1. *Simple diffusion*. Most exogenous chemical substances, particularly those of low molecular weight, gain access to the foetus by diffusion. Of importance here are the concentration gradient, the area of exchange across the placenta, the structural characteristics of the placental tissue to be crossed, and the physicochemical nature of the drug itself. These last include the size and spatial conformation of the molecule, its degree of ionization, lipid solubility, and extent of binding to macroprotein molecules. Drugs which are undissociated and highly lipid soluble diffuse most rapidly.

2. *Facilitated diffusion*. Some substances pass more rapidly across the placenta because facilitatory mechanisms exist at the cellular membrane level. An example of this would be facilitated diffusion of iron.

3. *Active transport*. Some drugs are actively transported across the placenta by a process which uses metabolic energy. An example of this is the diuretic triamterene.

4. *Transport of metabolites*. Some drug molecules are transported into the foetus only after metabolic transformation. An example would be ascorbic acid.

5. *Direct transport*. Occasionally the maternal and foetal circulations are in direct contact, as evidenced by passage of foetal erythrocytes into the mother and vice versa. This is an infrequent occurrence, and it probably does not play any important role in the transfer of drugs.

**Metabolic transformation of drugs in the placenta**

Within the placenta drugs can be metabolized, and such metabolic transformation may make the drug either more or less biologically active. There are four fundamental processes of biotransformation: oxidation, reduction, hydrolysis, and conjugation. Hydroxylation is a particularly important example of oxidative metabolism, hydrogenation of double bonds is an important example of reduction while the breaking of amide and ester bonds are hydrolytic reactions. The formation of glucuronides and sulphates are examples of conjugation reactions.

Trophoblastic cells of the placenta contain an abundance of endoplasmic reticulum, the cellular organelle where microsomal enzymes which perform these functions are situated. In the placenta all these reactions take place. Phosphatases liberate energy-rich phosphate bonds, sulphatases participate in the synthesis of oestriol, amino oxidase and catechol-O-methyltransferase inactivate biogenic amines, and peptidases modify polypeptides such as angiotensin, oxytocin, and ADH.

The effects of drugs on placental function are of significance. Some drugs can enhance enzymic activity in the placenta by induction, and others can inhibit enzymic activities such as those involved in steroid metabolism, particularly processes of aromatization. Other drugs reduce the utilization of glucose by the placenta and can thus modify a principal energy substrate utilized by the foetus.

**Distribution and transformation of drugs within the foetus**

The distribution of drugs in foetal tissue has been studied in experimental animals by autoradiography following administration of a radioactive drug. The large amounts of data thus obtained in different animal species suggest that the distribution of drugs in the foetus is similar to that in the adult organism. However, there are differences, particularly in early pregnancy. The blood-brain barrier develops late in foetal life, so the distribution of drugs in the foetus shows some important differences from that in the adult.

Some examples of selectivity of uptake in different foetal organs which have practical significance are those of chloroquine fixing in the retina, of streptomycin and other aminoglycosides fixing in the acoustic nerve, and of iodine and antithyroid drugs being taken up by the thyroid. Tetracycline is concentrated in bone tissue and in dentine. Drug metabolizing enzymes within the foetus increase gradually as the foetus matures. Several studies have been done on human foetal tissue from legal abortions. In human foetal liver, there is a high capacity for oxidation of drugs, while reductive transformations and

reduction in transformation in hydrolytic processes are often depressed. In the first and second trimester, the foetal liver has a glucuronyl transferase activity less than one tenth that of the adult. In the adrenal glands oxidation and demethylation are poorly developed, while metabolism by reduction is similar to that in the adult. In general, drug metabolism in foetal tissue is less well developed than that in the adult, and hence the capacity to detoxify drugs is greatly reduced. This is important, particularly in the neonate and more particularly in premature neonates where drugs may be very slowly eliminated.

To reduce transplacental passage of drugs when labour is imminent, it is important to avoid

(a) drugs which foetal enzyme systems are not efficient at coping with, such as those which must be glucuronidated;
(b) drugs which might displace bilirubin from plasma protein;
(c) drugs which may provoke physical dependence;
(d) drugs which are potentially myelotoxic;
(e) drugs which inhibit synthesis of prothrombin;
(f) drugs which reduce haemolysis in G6PD deficient individuals, such as sulphonamides, phenacetin, chloramphenicol, nitroturanes, and aspirin.

Some ill effects of drugs in pregnancy are only apparent in the neonate. Among these effects are paralytic ileus caused by ganglion blockers, central depression caused by sedatives, cortico-adrenal suppression caused by the corticosteroids, hypothyroidism caused by antithyroid drugs, congestion of upper airways by reserpine, and haemorrhage caused by coumarin anticoagulants.

Still other drugs may have a very long latency before they declare their ill effects. The most notable example is diethylstilboestrol, predisposing the female foetus to vaginal adenocarcinoma but only manifested in adolescence.

### Teratogenic effects of drugs

Congenital malformations caused by drugs are much feared but are probably very infrequent. It has been estimated that 3% of all malformations are due to exogenous causes, such as infections, gamma radiation, and drugs. In fact, there are very few drugs which are able to produce malformation in human pregnancy. Such parameters as gestational age, type of drug, genetic background, dose, and time of administration are all important.

### Gestational age

(a) The blastocyst, prior to implantation, is relatively resistant to damaging agents, and it is commonly held that the blastocyst is either unharmed by the drug or killed by it.
(b) During the period of organogenesis, from the third to tenth week of pregnancy, the type of malformation caused by a drug is critically dependent on gestational age. Each organ has a period of maximum sensitivity, generally

corresponding to the most rapid phase of development and the most intense differentiation. However, many organs develop simultaneously, and hence multiple malformations are possible.

(c) After the first trimester most organs have already been formed, with the exception of the genital apparatus. This remains still sensitive to teratogenic agents. The central nervous system matures gradually in the latter half of pregnancy, and so psychotropic drugs and sex hormones are able to produce modifications of postnatal behaviour and of gonadotrophin secretion by an action late in pregnancy.

### Nature of the drug

Some drugs are selectively taken up by the foetal organs and hence cause selective malformations. Examples are lesions of the acoustic nerve caused by streptomycin and lesions of the limbs caused by thalidomide.

### Genetics of the foetus

The genetic background of the foetus is extremely important. It modifies the gravity, localization, and frequency of malformations.

Animal species differ in their response to teratogenic agents. Herein lies the problem of teratogenicity tests in animals and their non-applicability to man.

### Dose and time of administration

Teratogenic effects are very dependent upon dose and on duration of administration. A single dose may be either more or less damaging than repeated doses because of such effects as enzyme induction.

Some drugs have an effect on the gametes, usually during gametogenesis. Drugs with mutagenic effects of this sort include cytotoxic drugs, cinchona alkaloids, and podophyllum. Ionizing radiation has a similar effect.

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# Using this book

This book has been designed so that it can be readily consulted by clinicians on the use of therapeutic drugs in pregnancy. It gives information on possible teratogenic effects of all drugs in current use. For each drug the pharmacological actions are briefly described, as well as the effects on human pregnancy and lactation. A summary of animal pharmacology during pregnancy is included.

We wish to emphasize:

(1) that the information given in this book is not to be regarded as absolute;
(2) that data from experimental animals cannot be directly applied to man.

The drugs are listed according to pharmacological type and therapeutic use, grouping together drugs with similar clinical indications. In addition to the general names of the drugs (which are indexed) we have included chemical formulae and molecular weights, so as to precisely characterize them. Some proprietary names are included.

Each chapter (for example, 'General anaesthetics') includes a list of the drugs discussed in that chapter, with a codification of the recommendations for the use or non-use of each drug. The codes used are:

NC: Drugs not contra-indicated either in pregnancy or labour, when used in the normal therapeutic doses.

P: Precaution – drugs to be used with care, and only when absolutely necessary.

C: Drugs that are contra-indicated. Their use should be limited to cases of exceptional difficulty, and when recourse to other less contra-indicated drugs is not possible. In some instances, the drugs are absolutely contra-indicated in only certain stages of pregnancy (trimesters 1,2,3), in labour, or during lactation.

The entry relating to a particular drug starts with a single-sentence summary of recommendations. Where there is contra-indication, or the need for precaution, there follows a table showing the appropriate codes (C or P) and the stages to which they apply. Blanks in the table, or indeed the absence of a table, imply that the drug is not contra-indicated. Further detail is given in the text.

For some drugs we have found no information on clinical experience or animal experiments. The entries for these drugs are collected together at the

ends of the relevant chapters or sections of chapters: they are collectively preceded by a row of asterisks * * * * * * * * * * * * * * * * *

**Comparative table of embryonic development in diverse animal species. Compilation of data existing in current literature.**
Gestational age is expressed in days (weeks).

| | Man | Rat | Mouse | Rabbit | Chicken |
|---|---|---|---|---|---|
| Duration of pregnancy | 280 (40) | 22 (3.1) | 19 (2.7) | 33 (4.7) | 21 (3) (incubation) |
| Implantation of blastocyst | 7 (1) | 5-6 (0.7-0.9) | 7 (1) | 6 (0.9) | – |
| Initiation of cardiac action Pronephros | 22 (3.1) | 10 (1.4) | – | – | 1.5 (0.2) |
| Mesonephros | 25 (3.6) | 12 (1.7) | 9.5 (1.4) | – | 1.75 (0.25) |
| Thyroid outline | 27 (3.9) | 10 (1.4) | 8.5 (1.2) | – | 1.8 (0.25) |
| Outline of upper limbs | 27 (3.9) | 10.5 (1.5) | 9.3 (1.3) | 10.5 (1.5) | 2.2 (0.3) |
| Outline of metanephros Outline of lungs | 28 (4) | 12.2 (1.75) | 9.6 (1.4) | – | 3 (0.4) |
| Outline of lower limbs | 30 (4.3) | – | 10.3 (1.5) | 11 (1.6) | 2.5 (0.4) |
| Initiation of ossification | 41 (5.9) | 17.5 (2.5) | 12.5 (1.8) | – | 8 (1.1) |
| Outline of ducts of Müller | 40 (5.7) | 13.5 (1.9) | – | | 4 (0.6) |
| Outline of testicles | 45 (6.4) | 14.5 (2.1) | – | 20 (2.9) | 5.5 (0.8) |
| Closure of palate | 57 (8.1) | 16.5 (2.4) | 15 (2.1) | 19.5 (2.8) | – |

# Table of Contents

# Part 3

# Diuretics

## 1. DIURETICS

The diuretics are drugs which increase urine flow and modify the excretion of solutes. They are classified on the basis of their chemical structure and their mechanism of action.

THIAZIDE DIURETICS – these inhibit sodium and chloride reabsorption in the convoluted proximal tubule and increase excretion of potassium in the distal tubule. They also have an antihypertensive effect and reduce glomerular filtration.

MERCURIAL DIURETICS – these depress active reabsorption of sodium, and are dependent for their intensity of action on urinary pH.

INHIBITORS OF CARBONIC ANHYDRASE – these diminish bicarbonate reabsorption and reduce intra-ocular pressure.

INHIBITORS OF ALDOSTERONE.

OSMOTIC DIURETICS – these readily pass through the glomerulus and are not reabsorbed in the tubules.

MISCELLANEOUS DIURETICS

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During pregnancy diuretic therapy is used both in the presence and absence of E.P.H. gestosis. The following diuretics are discussed:

| | | |
|---|---|---|
| Quinethazone | P | 9 |
| Fenquizone | P | 10 |
| *Mercurial diuretics* | | |
| Meralluride | C | 11 |
| *Inhibitors of carbonic anhydrase* | | |
| Acetazolamide | P | 11 |
| Dichlorphenamide | P | 13 |
| Ethoxyzolamide | P | 14 |
| *Inhibitors of aldosterone* | | |
| Spironolactone | NC | 15 |
| *Osmotic diuretics* | | |
| Mannitol | NC | 16 |
| *Miscellaneous diuretics* | | |
| Clopamide | NC | 17 |
| Clorthalidone | NC (P during lactation) | 18 |
| Frusemide | NC | 19 |
| Mefruside | NC | 19 |
| Triamterene | NC | 20 |
| Ethacrynic acid | NC | 21 |

The thiazide diuretics should be used with care in the last trimester, in labour, and in the puerperium, because of possible disturbances of electrolyte balance, myelotoxicity in the neonate, and an inhibitory effect on lactation.

The mercurial diuretics are in fact little used, and are contra-indicated because of their toxicity.

The carbonic anhydrase inhibitors must be used with care in the last trimester because they can alter acid–base and electrolyte balance in the foetus and the neonate. Some experimental data, which have been confirmed in man, suggest a possible teratogenic action when carbonic anhydrase inhibitors are administered during embryogenesis.

Aldesterone inhibitors, osmotic diuretics, and the miscellaneous group which have various chemical structures, are not contra-indicated in pregnancy at normal therapeutic doses.

## 1.1 Thiazide diuretics

### *Chlorothiazide*

Saluric, 6-chloro-7-sulphamyl-1, 2, 4-benzothiodiazine-1, 1-dioxide (MW 295.74)

| ADMINISTRATION | PREGNANCY Trimester | | | LABOUR | LACTATION |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | | |
| Acute | | | | | |
| Chronic | | | P | | |

To be used with care in pregnancy.

Chlorothiazide is the principal benzothiazide derivative, and its mechanism of action is by means of inhibition of sodium and chloride reabsorption in the convoluted proximal tubule. Its efficacy is not diminished by variations in acid–base equilibrium, as occurs with acetazolamide or the mercurial diuretics. Chlorothiazide also has an antihypertensive effect, reduces elimination of uric acid, causes hyperglycaemia, and exacerbates diabetes. It is used in the treatment of oedema, nephrosis, diabetes insipidus, and in pregnancy.

Chlorothiazide crosses the placental barrier [1, 12, 13, 16] and passes into breast milk [5,7]. No cases of teratogenicity have been observed [3, 4] which could be linked to the use of the drug in pregnancy. It has, however, been claimed that chlorothiazide can cause thrombocytopoenia in the neonate, as do other thiazides, if taken in the last trimester [2,11,14,17]. Following prolonged use, metabolic disturbances may appear (hyponatraemia, hypokalaemia, hyperglycaemia) in pregnant women [5, 6, 7, 15, 16]. The foetus appears to be relatively resistant to variations in maternal electrolytes, even although the occasional case of foetal hyponatraemia has been reported [6].

In the rat, subcutaneous doses of 250 mg/kg from the 10th to the 11th day of pregnancy, and doses of 166 mg/kg from the 8th day to the end of pregnancy, were not teratogenic [9,10].

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