Prescribing in Pregnancy

Fourth edition

Edited by

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Preface

The use of drugs in women who are pregnant or breast feeding is a question of fine balance. Harm may befall a baby because a drug has been used, but mother and baby could suffer if a disease goes untreated. Information about the safe and effective use of drugs in pregnancy has not kept pace with the advances in other areas of therapeutics. Systematic research involving drugs in pregnancy is fraught with ethical, legal, emotional and practical difficulties and in many cases our knowledge is based on anecdote or small studies.

The purpose of this book is to bring together what is known about prescribing in pregnancy and to put that information in a clinical context. The first three editions were well received and this has encouraged us to produce a fourth edition. All chapters have been extensively revised or rewritten, with several new authors bringing their clinical experience of this challenging subject.

We would like to thank Louise Sabir who once again has done much behind-the-scenes work in contacting authors.

Acknowledgement

Dr Weller died suddenly while training for the London Marathon shortly after submitting his chapter. He had also contributed to the third edition and we gratefully acknowledge the professional manner in which he approached these tasks.

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Margaret Ramsay
Nottingham
CHAPTER 1
Identifying fetal abnormalities
Lena M. Macara

Key points
• Days 18–55 postconception is the time of maximal teratogenic potential when most organs are differentiating
• Teratogenic effects of medications may affect both organ structure and organ function
• Detailed ultrasound assessment of the fetus by trained personnel should detect most major structural abnormalities, but minor abnormalities are often undetected
• Patients at risk of neural tube defects (NTDs) should have 5 mg of folic acid daily for a minimum of 6 wk prior to conception

Introduction
It is estimated that 2–3% of all pregnancies in the United Kingdom are affected by congenital abnormality. Almost half of these abnormalities remain of uncertain aetiology, a further 25% may be linked to a variety of genetic problems and only 2% are likely to be associated with environmental factors that include medicinal products.

While this is a very small proportion of all birth defects, it is a critical group, since the avoidance of some medications will prevent these abnormalities from occurring. For parents and physicians, it is therefore one of the few areas in which the outcome of pregnancy can be influenced.
Both the number and spectrum of medicinal products available, ‘over the counter’ and on a prescribed basis, has expanded enormously in the last decade. At any given time, over 80% of women in childbearing years are using some type of medication and around 50% of pregnant women are prescribed a medication other than a vitamin or supplement during pregnancy [1,2].

This chapter aims to guide clinicians on normal pregnancy development, the options currently available to assess fetal development in utero and the spectrum of abnormalities linked with drug use during pregnancy, which may be detected prior to delivery. The following chapters will provide guidance on prescribing in pregnancy, highlighting those drugs that should be avoided in pregnancy and offering direction on those medications with least risk to the pregnancy while ensuring that the underlying medical issues are dealt with.

**Embryonic and fetal development**

It is clear from practice that not all drugs affect a pregnancy in an identical manner or to equal degrees of severity. This is due to the rapid but staggered sequence of events that occur as two cells quickly multiply to form the embryo and fetus we recognise. Understanding the order and timing of this process may help us to understand which organ systems are likely to be affected at each stage of pregnancy and anticipate the possible long-term effects which may ensue.

Fetal development can be divided into three main stages: the pre-differentiation or pre-embryonic phase; from conception until 17 days postconception, just after the first missed period; the embryonic stage from 3 to 8 weeks postconception and the fetal phase from week 8 until term.

During the pre-differentiation stage, the cells of the conceptus divide rapidly and remain totipotent. Any insult to the pregnancy during this phase seems to have an ‘all or nothing’ effect. If most of the cells are affected, the pregnancy is spontaneously miscarried but when only some cells are affected, the remaining totipotent cells appear to replace the damaged cells without any apparent long-term deleterious effect. Most women will not yet have missed their first period and therefore may not realise that they are pregnant.

During the embryonic period, these cells differentiate and form definitive organ systems (Figure 1.1). Since the cells have now
Identifying fetal abnormalities

<table>
<thead>
<tr>
<th>Main Embryonic Period (wk)</th>
<th>Fetal Period (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  2</td>
<td>3  4  5  6  7  8  9  16  32  38</td>
</tr>
</tbody>
</table>

- Period of dividing zygote, implantation and bilaminar embryo
- Embryonic disc
- Morula
- Amnion
- Blastocyst
- Not susceptible to teratogenesis
- Death of embryo and spontaneous abortion common
- Neural tube defects (NTDs)
- Mental retardation
- CNS
- TA, ASD and VSD
- Heart
- Amelia/meromelia
- Upper limb
- Amelia/meromelia
- Lower limb
- Cleft lip
- Upper lip
- Low-set malformed ears and deafness
- Ears
- Microphthalmia, cataracts, glaucoma
- Eyes
- Enamel hypoplasia and staining
- Teeth
- Cleft palate
- Palate
- Masculinisation of female genitalia
- External genitalia
- TA, Truncus arteriosus; ASD, Atrial septal defect; VSD, Ventricular septal defect

**Figure 1.1** The timing of fetal development. Critical time periods for development of organ systems. Reprinted from Figure 8.15 from Moore et al: The Developing Human: Clinically Oriented Embryology, 6/E ©1998 with permission from Elsevier
differentiated, if they are extensively damaged, permanent effects are likely to occur in the end organ. Although the embryonic period is short, each end organ has a window of maximal susceptibility when the teratogenic insults are likely to be most severe. In some circumstances, the effects may be dosage dependent.

The fetal period is primarily a time of growth and maturation, and most drugs are therefore unlikely to cause significant structural defects. However, organs such as the cerebral cortex, the gastrointestinal tract and the renal glomeruli continue to differentiate and develop throughout pregnancy and into the neonatal period. These organs therefore remain vulnerable to growth or functional damage by medicinal products during the later stages of pregnancy. These are often more subtle changes and frequently will only become evident as the neonate grows and develops. The teratogenic effect of a drug administered during pregnancy may therefore be easily overlooked.

Since the nature and degree of teratogenic effects on a pregnancy is largely determined by the stage of development at which exposure occurs, the gestational age of the pregnancy at presentation must first be determined. Thereafter, careful documentation of the nature, dosage and duration of the products used should be recorded for future reference.

Determining gestational age in pregnancy

The pregnancy hormone human chorionic gonadotrophin can be detected in urine around the time of the first missed period, and in serum even earlier. Transvaginal ultrasound (TV) can now visualise a pregnancy 2–3 weeks following conception, though viability of the pregnancy can only be determined once a fetal heartbeat is seen 3–4 weeks postconception by TV scan or 4 weeks postconception with an abdominal ultrasound scan. Thereafter, standard measurements of the total fetal length, fetal femur length and fetal skull diameter may be obtained to calculate the gestational age of the fetus. Pregnancy is divided into three trimesters: the first trimester from the time of the last menstrual period, week 0 until week 12, the second trimester from week 12 until week 24 and the third trimester from week 24 until term.

Evaluating fetal anatomy

With good quality ultrasound machinery, basic fetal anatomy, confirming integrity of the skull bones, the abdominal wall, upper
and lower limbs, and a fetal stomach, may now be identified by the 12th week of gestation. Many units also assess the depth of nuchal fluid present at the fetal neck (Figure 1.2). This, in combination with biochemical parameters, can quantify the risk of chromosomal abnormality. In addition, a large nuchal measurement (Figure 1.3) is associated with increased risk of fetal cardiac abnormality, and detailed assessment of the heart at a later gestation is advised. A more extensive examination of fetal anatomy in the first trimester is performed in selected units. At 11–12 weeks,
a complete examination of the fetus can be achieved in only 50–60% of cases. With the addition of TV examination, and deferring the examination until 12–14 completed weeks of pregnancy, 90% of pregnancies can be successfully examined [3,4]. While this option offers early reassurance to parents, most departments do not have the trained personnel, nor the resources to offer this level of detailed ultrasound examination in the first trimester.

For the majority of patients, fetal anatomy is still evaluated between 18 and 20 weeks of gestation – ‘the routine anomaly scan’. Though this is recommended for all pregnancies, at the time of writing, routine anomaly scans are still not available within some major health board areas in Scotland and England unless specific indications such as medication in pregnancy are highlighted.

Many groups have evaluated second trimester ultrasound examination and confirmed that 70–90% of significant abnormalities should be detected [5,6]. There are several reasons for this variation. The list of structures that are deemed essential to examine in each pregnancy is at the discretion of individual units, and many departments do not examine the fetal heart, face or limbs in detail. Therefore an examination may be complete as per department protocol but may not evaluate the very organ most likely to be affected by specific drugs. In addition, some anomalies such as congenital diaphragmatic hernia, microcephaly and hydrocephalus may not be evident until the late second trimester, after the time of a standard detailed scan, and other functional problems of organs like the brain or kidney will remain unidentified until the neonatal period. Moreover dysmorphic features, such as flatting of facial bones or other soft markers, will not be seen on standard ultrasound scans.

In view of these facts, women who are at risk of congenital abnormality as a result of medication during pregnancy must be highlighted at every stage of referral to ensure that a full detailed ultrasound examination is performed, and at times repeated, at an appropriate stage of pregnancy.

Within the last couple of years, 3D ultrasound technology has enabled more detailed examination of the fetal surface and proved particularly useful in assessment of the fetal face (Figure 1.4). Three-dimensional images often prove very difficult both to obtain and to interpret at less than 24 weeks of gestation. Where exclusion or confirmation of fetal problems such as cleft lip is required, referral to a tertiary centre with 3D ultrasound experience may be indicated.
Identifying fetal abnormalities

Figure 1.4 Three-dimensional ultrasound image of a normal fetal face (24 weeks of gestation).

Once a fetal abnormality has been identified on ultrasound, further information may be obtained from fetal MRI studies. To date, these studies are primarily a research tool, evaluating, for example, if MRI can predict the severity of spina bifida or the degree of fetal lung development in congenital diaphragmatic hernia.

Pregnancy management

Pre-pregnancy: reducing the risk of fetal abnormality

Ideally all pregnancy management should commence in the preconception period. Clinicians need to be aware of the potential effects of the more commonly prescribed medications as outlined in Table 1.1. Where possible, non-essential drugs should be stopped and polypharmacy reduced to a monotherapy, selecting those with the least teratogenic profile. Women on antihypertensive and anticonvulsant therapy, on treatment for long-standing rheumatoid problems and on anticoagulants and immunosuppressants should meet with their clinician to optimise drug therapy prior to conception. As evident from Figure 1.1, much of critical organ development will occur before most women attend for a booking appointment, and therefore stopping any drug abruptly at week 10–12 is of little value to either the woman or her fetus. The risk of
Table 1.1 Medications associated with specific congenital abnormalities

<table>
<thead>
<tr>
<th>Fetal effects</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>Neural tube defects (spina bifida,</td>
<td>Sodium valproate, hydantoin, rifampicin</td>
</tr>
<tr>
<td>anencephaly, encephalocele)</td>
<td></td>
</tr>
<tr>
<td>Other structural defects</td>
<td>Retinoids, warfarin, carbamazepine, sodium</td>
</tr>
<tr>
<td></td>
<td>valproate</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>Anti-epileptics, alcohol</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Lithium, thalidomide, retinoids, paroxetine</td>
</tr>
<tr>
<td>Renal</td>
<td>valproate</td>
</tr>
<tr>
<td>Oliguria, renal failure</td>
<td>NSAIDS, ACE inhibitors, COX-2 inhibitors</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td>Augmentin, NSAIDS</td>
</tr>
<tr>
<td>Gastoschisis</td>
<td>Cannabis, recreational drugs</td>
</tr>
<tr>
<td>Facial</td>
<td></td>
</tr>
<tr>
<td>Cleft lip and palate</td>
<td>Rifampicin, retinoids, steroids</td>
</tr>
<tr>
<td></td>
<td>Sodium valproate, benzodiazepines</td>
</tr>
<tr>
<td>Abnormal facial features</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Thalidomide, cocaine, tetracyclines</td>
</tr>
<tr>
<td>Growth restriction</td>
<td>β-blockers, alcohol, valproate, amphetamines</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>Aspirin, warfarin, crack cocaine</td>
</tr>
</tbody>
</table>

NTDs in pregnancy can be reduced by the use of high-dose folic acid. In order to be effective, 5 mg of folic acid must be taken for at least 6 weeks prior to conception and continued until the 12th week of pregnancy. Any woman of childbearing age who is on medication associated with a risk of NTD should be prescribed this higher dose of folic acid [7,8]. Folic acid may also reduce the risks of facial clefting in patients on anticonvulsant therapy, but this is based on less clear data [9].

**Antenatal care: assessing fetal development**

Once pregnancy is confirmed, the patient should be referred to an obstetric unit for antenatal care. Having confirmed gestational age and basic fetal anatomy, a full detailed ultrasound scan should be arranged in the second trimester. The presence of an increased nuchal measurement should stimulate a detailed examination in the second trimester, with particular attention to the fetal heart.
Identifying fetal abnormalities

Figure 1.5  (a) A normal mid-sagittal image of a 12-week fetus with normal cranial bones (C) visible;  (b) a 12-week fetus with anencephaly. The cranial vault is absent and fetal brain tissue (B) seen to float freely.

**Antenatal care: common fetal abnormalities detected by ultrasound**

**Central nervous system**
Failure of the neural tube to close may result in a range of defects. Anencephaly, failure of the skull bones to develop, is incompatible with independent life and should be detected in all pregnancies by 12 weeks of gestation, if the skull bones are not clearly visualised on ultrasound (Figures 1.5a–1.5b). Although spina bifida
usually affects the lower vertebrae, up to 80% of babies will also have intracranial signs in the second trimester, due to an abnormal cerebellum and hydrocephalus (Figure 1.6). With current ultrasound imaging, amniocentesis, to detect the acetyl cholinesterase band specific for NTD, should no longer be required. Over 90% of NTDs should be detected with second trimester ultrasound assessment. Other abnormalities such as Dandy–Walker-type malformations (Figure 1.7) and cerebral cysts should be detected antenatally.

**Cardiovascular system**
Even in specialist units where the heart and outflow tracts are examined, 70–80% of abnormalities are identified antenatally, but detection rates as low as 15% have been reported in more general population studies [10,11]. When a normal four-chamber view of the heart is seen (Figure 1.8), 40% of anomalies should be excluded.

**Facial clefting**
The fetal position, the small size of the alveolar ridge, fetal limbs placed in front of the face and the increasing maternal body mass index in the population can make this a technically difficult area
Figure 1.7 Ultrasound of a fetal head. A large echolucent area (Dandy–Walker (DW)-type malformation) is present in the posterior fossa.

to examine completely. When complete views of the face are obtained, 50–70% of cleft lip with or without cleft palate is recognised (Figures 1.9a–1.9b). Isolated cleft palates have not been detected prenatally, most probably because the fetal tongue, of the same echogenicity as the palate, occludes the defect.

Figure 1.8 A normal four-chamber view of the heart showing the ventricles (V) and atria (A).
Figure 1.9 (a) Normal profile of fetal lips (L) in the second trimester; (b) profile of fetal lips showing the upper lips (L) with a large cleft (C) present.

Other craniofacial abnormalities such as hypertelorism or a thin upper lip cannot be identified with current 2D scan imaging. With increasing experience of 3D imaging, these ‘minor’ soft markers may well be visualised, but the value of obtaining this information, particularly in the third trimester may be questionable.