Scientific Basis of Obstetrics and Gynaecology

Edited by

Ronald R. Macdonald

SECOND EDITION

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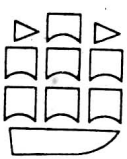

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Preface to the Second Edition

The purpose of the first edition was to offer trainee and established clinicians a lucid explanation of new scientific fields and of the areas of progress which had direct application in clinical practice. Selected topics were discussed in depth, from terminology and basic principles through the new information to the clinical application.

Reflecting current attitudes the second edition has inclined a little more towards the *application* of new basic science information, rather than dwelling on basic trends themselves. Thus Professor Whitfield's concise exposition of rhesus theory and management will be valuable as long as there remains a reservoir of sensitised women. The rest of his chapter on amniotic fluid reviews the application of lecithin estimations in the management of maturity problems. Similarly the chapter on Sexual Dysfunction should be seen as a sequel to Human Sexual Behaviour in the first edition, and illustrates the application of basic knowledge in this field to a regular clinical service.

For the second edition ten of the previous topics have been retained because of further progress in those fields, and the need for extensive revision of each chapter is an indication of the pace of progress and the amount of new information to be assimilated. The remaining chapters are entirely new, on topics which had to be omitted from the first edition or which have emerged with new ideas requiring the same treatment. All the chapters are by acknowledged experts in their own field, who were invited to contribute because of their ability to write with authority, clarity and enthusiasm.

A special effort has been made to produce the book as quickly as possible, consistent with quality production, in order to ensure that the information is as up-to-date as possible. For this edition selected references have been given in full, to clarify the point of reference and to assist further study as desired.

The success of the first edition has confirmed the need to bridge the gap between basic scientific progress and clinical application. We hope our second edition proves similarly helpful.

1977 Ronald R. Macdonald

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The 'baby and hands' motif is from the Leeds Medical School brochure by permission of the University of Leeds. The original drawing was by Mr H. Grayshon Lumby who also prepared the illustration of feto-placental oestrogen biosynthesis in Chapter 5.

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1. Amniotic Fluid

C. R. Whitfield

PHYSIOLOGICAL CONSIDERATIONS

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Amniotic fluid volume

AMNIOTIC FLUID ANALYSIS IN THE MANAGEMENT OF RHESUS HAEMOLYTIC DISEASE

Spectrophotometric measurement of amniotic fluid bilirubin—prediction of severity
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AMNIOTIC FLUID ANALYSIS IN THE ESTIMATION OF FETAL MATURITY

Fetal ageing, growth and physiological maturation
Amniotic fluid indices of fetal maturation
Fetal pulmonary surfactant
Methods for measurement of fetal pulmonary surfactant in amniotic fluid

1. Lecithin:sphingomyelin ratio
2. Bubble stability test
3. Gas–liquid chromatographic methods

Changes in surfactant production—antepartum, intrapartum and neonatal
Clinical applications

AMNIOCENTESIS

Techniques—preliminary sonar—amniocentesis clinics
Complications

The antenatal diagnosis of fetal neural tube defects and genetic disorders by analysis of amniotic fluid or its cells is described in Chapter 10, but some observations on the technique of amniocentesis during early as well as in advanced pregnancy will be made in this chapter.

PHYSIOLOGICAL CONSIDERATIONS

Formation and turnover of amniotic fluid

The composition, turnover and volume of amniotic fluid (AF) depend on exchanges of molecular water and electrolytes between the fetal and maternal plasma and the AF, occurring across the fetal skin and membranes, and also on bulk flows—inflows due to fetal micturition, and to a lesser extent from its respiratory tract, and outflows resulting from fetal swallowing. As recently and very usefully reviewed by Lind (1975), the relative importance of diffusion and of this system of opposing bulk flows alters progressively from early pregnancy to term. It is also possible that the fetal membranes (Fig. 1.1) may be actively involved in the formation of the AF. There are columnar

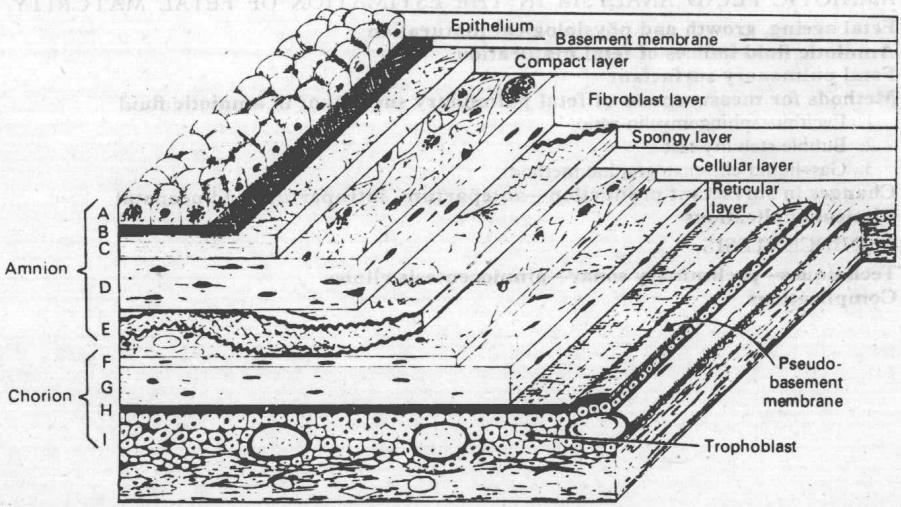

Fig. 1.1 Diagram of the fetal membranes, showing differentiation of the amnion into five separate layers—cuboidal epithelium and its adherent basement membrane, a compact and relatively strong reticular layer, a loose fibroblastic layer and a spongy layer of connective tissue which enables the amnion to slide over the underlying chorion. The four layers of the chorion are also shown—cellular, reticular, pseudobasement membrane and trophoblast. Reproduced by kind permission from Bourne, G. L. (1960) *American Journal of Obstetrics and Gynecology*, **79**, 1070–1073.

cells with secretory features in the amniotic epithelium during early pregnancy, but, as progressive differentiation into five separate layers occurs, these secretory cells disappear and the amnion has become avascular when the turnover of AF is maximal. It seems likely, therefore, that any direct

contribution by this membrane to the AF is relatively unimportant and must be restricted to early pregnancy.

Until increasing stratification and keratinisation reduces significantly the permeability of the fetal skin, AF is derived mainly as a filtrate of fetal plasma by diffusion across the skin. During early pregnancy its composition therefore resembles closely that of fetal extracellular fluid; marginally lower sodium and slightly higher urea concentrations in the AF than in fetal plasma are due to the intermittent passage of very small amounts of hypotonic urine by the fetus from the end of the first trimester. In contrast, there are significant (opposing) concentration gradients for sodium and urea between the AF and the water phase of maternal plasma which also has significantly different chloride and potassium concentrations.

During the first half of pregnancy, the volume of AF is closely related to fetal and placental weights and to gestational age, the closest correlation being with the fetal weight and thus with fetal growth and increasing surface area; this is consistent with the concept that at this stage AF arises mainly by diffusion across the fetal skin. Direct measurement of AF in several series of women undergoing therapeutic abortion, and also early gestational sac volume measurements by sonar (Robinson, 1975), shows a narrow range of values that increases from almost 5 ml at 6 weeks to about 30 ml at 10 weeks and then more rapidly to about 350 ml at 20 weeks when the fetus weighs approximately 300 g.

When the fetal skin becomes impermeable the AF is, to use Lind's phase, 'exteriorized' from the continuum of water and electrolytes in the fetal extracellular body fluids. As a result, a close relationship is no longer maintained between the concentrations of electrolytes and other diffusible substances (and therefore of osmolality) in fetal extracellular fluid and in the AF. From about 20 weeks to term, AF osmolality and sodium concentration are reduced steadily and the concentration of creatinine and urea increase. Probably because small amounts of hydrochloric acid reach the AF from the fetal stomach, the concentration of chloride does not fall in parallel with that of sodium while potassium values remain constant. There is, however, continued simple diffusion in both directions across the fetal membranes, presumably mainly the amnion covering the placenta, so that AF is far from being a relatively static pool apart from the intermittent bulk flows of fetal micturition and swallowing. Towards term, AF water is probably replaced about every three hours by the constant exchange with the mother of as much as 500 ml of water per hour. Some of the water exchange between the AF and the mother occurs via the fetus; in addition to diffusion across the fetal surface of the placenta, absorption of water from the AF to the fetus via the umbilical cord has been demonstrated as early as 18 weeks (Abramovich, 1973) and water exchange across the cord may eventually reach a rate of 50 ml hourly (Plentl, 1961).

Presumably as a result of these processes of diffusion, abnormal biochemical changes in the maternal blood may be reflected in the AF; for example, AF bilirubin may be increased when a mother has marked hyper-

bilirubinaemia as a result of severe haemolytic anaemia. Similarly, certain drugs administered to the mother, including some antibiotics, may reach the AF.

From mid-pregnancy the fetal kidneys provide increasing bulk inflows, which by term reach at least 500 ml per day, and the tidal flow of fluid in the trachea results in a net episodic inflow of fetal lung fluid that may possibly amount to 100–200 ml daily. The biochemical composition and osmolality of the AF are at this stage very similar to those of dilute fetal urine, with the addition of phospholipids and other substances from the developing fetal lung and of cells shed from the fetal skin. The fetal lachrymal, salivary, sweat and sebaceous glands also begin to make very small contributions to the composition of the AF, while in the female fetus desquamation of vaginal cells may alter the cytological profile of the liquor.

Amniotic fluid constituents

In recent years the biochemistry of the AF has been a subject of increasing interest and study, but much of the information gained has no clinical application so far and the normal values and trends of many constituents of potential practical value have yet to be established with certainty. In addition to cytology and to the cytogenetic and biochemical testing of cultured AF cells, electrolytes and gas tensions, proteins and aminoacids, hormones and enzymes, prostaglandins and other lipids, and the products of both haemoglobin breakdown and of fibrin degradation have all been studied in the AF itself—the interested reader is referred to the recent comprehensive volume edited by Fairweather and Eskes (1973). Details of some of the more

Table 1.1 Changes in some amniotic fluid constituents. Normal values, based on composite data from various sources including the author's own material (mean values except where otherwise indicated).

	16 weeks	34–36 weeks	
Osmolality (mOsm/kg)	275	265	Continued decrease to term
Sodium (mmol/l)	136	132	Continued decrease to term
Urea (mmol/l)	2·8	3·8	Continued increase to term
Creatinine (μmol/l)	44	132	Continued increase to term
Bilirubin (ΔOD at 450 nm)	0·03–0·18	0·01–0·06	Continued decrease to term (often to undetectable levels). Maximum (0·055–0·195) at 22–26 weeks
Total protein (g/l)	4·0	3·0	Continued decrease to term. Maximum values (4·7–8·0) at 24–28 weeks
Alphafetoprotein (mg/l)	10·0–40·0	0·5–5·0	Progressive fall from end of first trimester to term
Lecithin (mg/l)	20	30–100	Terminal increase
Cytology	Small numbers of mostly large anucleate cells	Increasing numbers of fetal epidermal cells	Terminal increase in lipid-containing cells in most patients

important constituents, at the time that amniocentesis is likely to be performed for genetic diagnosis (approximately 16 weeks) and in late pregnancy (34 to 36 weeks) are shown in Table 1.1, illustrating the changing composition of the AF.

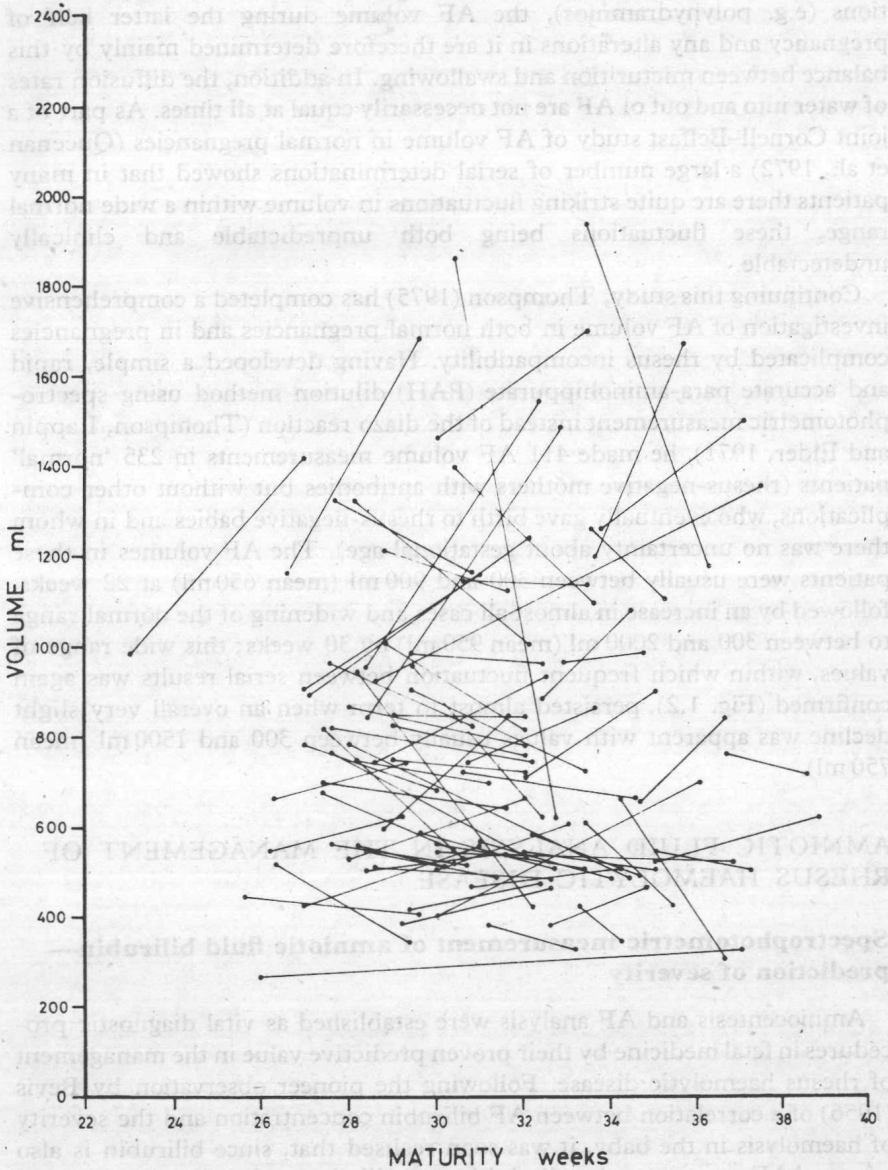

Fig. 1.2 AF volumes plotted against gestational maturity, showing two serial measurements in each of 74 normal pregnancies of sure gestational age; in addition to illustrating the wide range of normal values referred to in the text, the variation in the trend between serial measurements in individual patients is apparent. Reproduced by kind permission from Thompson, W. (1970) *M. D. Thesis*, The Queen's University of Belfast.

Amniotic fluid volume

After mid-pregnancy the increasing bulk inflows from the fetal urinary and respiratory tracts are usually more or less balanced by increasing fetal swallowing. Although other factors probably contribute in abnormal situations (e.g. polyhydramnios), the AF volume during the latter half of pregnancy and any alterations in it are therefore determined mainly by this balance between micturition and swallowing. In addition, the diffusion rates of water into and out of AF are not necessarily equal at all times. As part of a joint Cornell–Belfast study of AF volume in normal pregnancies (Queenan et al., 1972) a large number of serial determinations showed that in many patients there are quite striking fluctuations in volume within a wide normal range, these fluctuations being both unpredictable and clinically undetectable.

Continuing this study, Thompson (1975) has completed a comprehensive investigation of AF volume in both normal pregnancies and in pregnancies complicated by rhesus incompatibility. Having developed a simple, rapid and accurate para-aminohippurate (PAH) dilution method using spectrophotometric measurement instead of the diazo reaction (Thompson, Lappin and Elder, 1971), he made 411 AF volume measurements in 235 'normal' patients (rhesus-negative mothers with antibodies but without other complications, who eventually gave birth to rhesus-negative babies and in whom there was no uncertainty about gestational age). The AF volumes in these patients were usually between 300 and 900 ml (mean 650 ml) at 22 weeks, followed by an increase in almost all cases and widening of the normal range to between 300 and 2000 ml (mean 950 ml) by 30 weeks; this wide range of values, within which frequent fluctuation between serial results was again confirmed (Fig. 1.2), persisted almost to term when an overall very slight decline was apparent with values usually between 300 and 1500 ml (mean 750 ml).

AMNIOTIC FLUID ANALYSIS IN THE MANAGEMENT OF RHESUS HAEMOLYTIC DISEASE

Spectrophotometric measurement of amniotic fluid bilirubin—prediction of severity

Amniocentesis and AF analysis were established as vital diagnostic procedures in fetal medicine by their proven predictive value in the management of rhesus haemolytic disease. Following the pioneer observation by Bevis (1956) of a correlation between AF bilirubin concentration and the severity of haemolysis in the baby, it was soon realised that, since bilirubin is also a normal AF constituent that diminishes steadily (towards zero values) during the last trimester, rhesus prediction could be improved by relating the bilirubin value to the gestational age at the time of amniocentesis. Liley (1961) devised a simple spectrophotometric method for estimating AF

bilirubin, based on the difference between the actual optical density (OD) at 450 nm and the corresponding value of a baseline drawn between the OD readings at 365 and 550 nm (i.e. the ΔOD450 value; Fig. 1.3). He then established his three now widely used prediction zones (Fig. 1.4) from values obtained during more than 100 pregnancies and plotted (on a logarithmic scale) against the gestational age during the last trimester. He also showed that the upper and middle zones could usefully be subdivided, giving a total of five separate prediction zones. The practical value of these zones, which

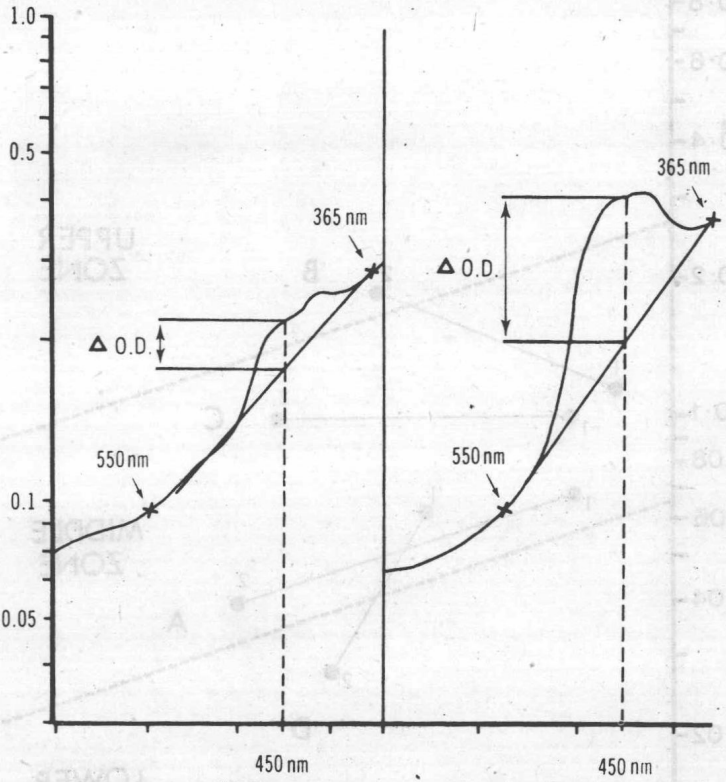

Fig. 1.3 Measurement of ΔOD at 450 nm, using a baseline drawn between the OD readings at 365 and 550 nm.

slope gently downwards towards term and thus provide an in-built correction for the decreasing amount of 'physiological' bilirubin, has been confirmed in several large series (e.g. Bowman and Pollock, 1965; Whitfield, Neely and Telford, 1968). When automatic linear recording spectrophotometers are used, the ΔOD450 should be measured after transcribing the readings at 365, 450 and 550 nm on to semilogarithmic paper. A further refinement, to allow for variations in the turbidity of different AF samples, is to calibrate the logarithmic scale so that the 450 nm peak always lies near the centre of the paper, and in any case each clinic should probably establish its own limits for the different prediction zones.

Other spectrophotometric methods have been devised, mostly based on