Obstetric Therapeutics

CLINICAL PHARMACOLOGY AND THERAPEUTICS IN OBSTETRIC PRACTICE

Edited by D. F. Hawkins

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Clinical Pharmacology and Therapeutics in Obstetric Practice

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Preface

In recent years the therapeutic aspects of obstetrics have developed to a point where they are a major part of obstetric practice, overshadowing relatively stereotyped surgical procedures in importance. The Royal College of Obstetricians and Gynaecologists in London has recognised this change and instituted a Part I examination for its Membership, requiring the future specialist to have knowledge of the physiology and pharmacology which form the basis of obstetric therapeutics. There is still a paucity of sources from which obstetricians in training can obtain consistent information on the therapeutics of their subject, in contrast to its surgery, which is thoroughly treated in the standard textbooks and well taught and practised by clinicians. Established obstetricians and teachers have found it necessary to acquire knowledge of newer therapeutic procedures piecemeal, often from their junior colleagues.

The present work provides in a unified form an account of the therapeutics of antenatal care, of the confinement and puerperium, of abnormal pregnancy and of obstetric emergencies. The book defines the field of obstetric therapeutics, dealing with the prevention and therapy of disorders arising primarily as abnormalities of pregnancy, not with the medical disorders which can complicate pregnancy. It represents a systematic approach to the therapeutics of obstetrics written by obstetricians, most of them of the newer generation, and is intended for postgraduate students of the speciality and those already in practice.

The first chapter is devoted to the clinical pharmacology of the human pregnant uterus. In subsequent chapters the pattern of A. J. Clark's 'Applied Pharmacology' has been followed, brief accounts of current views on basic physiology and pathology leading into discussions of available therapeutic measures. The chapters on the psychology and psychiatry of the pregnant woman, on obstetric physiotherapy, on neonatal therapeutics and on contraception will help to bridge the gaps caused by lack of understanding of the role of these disciplines in obstetrics. It is hoped that these sections will encourage obstetricians to utilise their full therapeutic potential.

Differences may be noted in the depth at which the topics of the various chapters are treated. This reflects imbalance in progress in aspects of the field and should serve to emphasise the need for clinical research along scientific lines in areas where development has been slow.

The inclusion of complete references is a subject which has given much concern, as they tend to interfere with smooth reading of the text. The editor feels that the current status and rate of change of medical knowledge is such that today there is little justification for ex cathedra dogmatism. The modern postgraduate student should be encouraged to require chapter and verse for statements and to learn to use medical libraries where appropriate. In addition, established practitioners have a right to know to which of their colleagues an opinion can be attributed. The insertion of names and dates in the text has been preferred to the numerical system. It may tend to break up the text, but it obviates frequent reference to the end of the chapter to determine sources.

The reader may discern a flavour of University College Hospital and Hammersmith Hospital in the book, and most of the authors and the editor owe much to the influence of the late Professor W. C. W. Nixon and to Professor J. C. McClure Browne. On the other hand these two great teachers must not be held responsible for views expressed, some of which they would have considered heretic!

I am grateful to Mrs Doreen Henderson and to Dr A. H. Labrum for helpful discussions when the book was planned, to Mr S. A. Reynolds for his patience and encouragement during its preparation, particularly to Miss Phyllis Holbrook for all the help she has given me with the editorial work, and to my wife and family for their tolerance over the last two years. Dr K. Fotherby's helpful comments on Chapter 3 were much appreciated and we are indebted to the authors and publishers of books and journals from which illustrations were copied or modified.

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September 1973

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The Pharmacology of the Pregnant Human Uterus

D. F. Hawkins

The pregnant uterus is a hollow muscular bag, constructed of a loose basket-work of bundles of smooth muscle fibres set in a connective tissue matrix. Much effort has been directed at describing the disposition of these bundles of fibres in detail. They are not arranged in layers, as in the intestine, but form an oblique three-dimensional lattice of criss-crossing spirals (Calza, 1807; Terruhn, 1927; Goerrtler, 1930). The points of practical functional significance are that in the uppermost part of the uterus, the bundles tend to embrace the fundus and that as they descend there is some tendency for the obliquity of the bundles to become more longitudinal in relation to the axis of the uterus. This disposition ensures the integrity of the fundus as uterine contractions occur, directing the mechanical retraction exerted by the fibres to act on the lower segment and cervix. It also ensures transmission of the waves of contraction, which tend to start at the fundus and travel down the uterus towards the cervix.

In the lower third of the uterus, the proportion of muscle fibres to connective tissue matrix is reduced. In the cervix the intrinsic muscle fibres are scanty, accounting for something of the order of 1% of the tissue, which consists largely of a collagenous network. Hughesdon (1956) describes bands of muscle fibres, extensions of the myometrium of the lower third of the uterus running down into the cervix (Figure 1A and B). It is unlikely that the bands of muscle are as discrete as those shown in the figure in all women—the muscle fibres may be diffusely distributed rather than in bundles.

The structural changes in the uterus which take place during pregnancy are accounted for by growth, by the increasing size of the conceptus, by

the progressive increase in spontaneous (Braxton-Hicks) contractions after midpregnancy and by the progressive softening of connective tissue in the lower part of the uterus and the cervix during the third trimester. As the myometrium of the corpus uteri grows, the scanty intrinsic muscle fibres of the cervix hypertrophy, but their function is probably limited to a tendency to maintain the cylindrical shape of the cervix—and perhaps assisting it to regain that shape as the uterus involutes in the puerperium. In the third trimester, it is now clear that there is considerable variation from woman to woman in the rate at which the increasing Braxton-Hicks contractions and softening of the matrix combine to retract muscle towards the fundus, with consequent thinning of the lower third of the uterus and

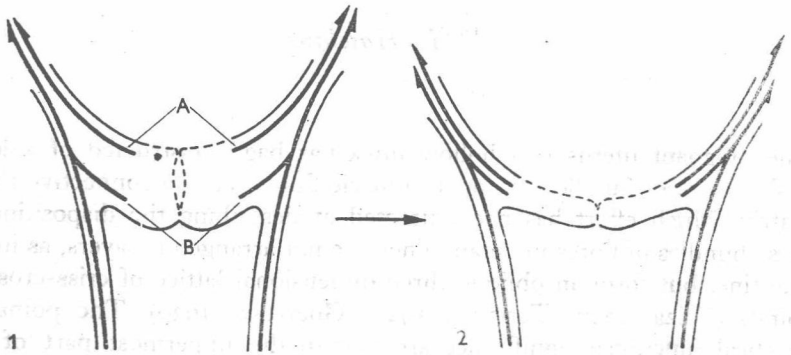

Figure 1. Muscle distribution in lower uterine segment, cervix and upper vagina. The fine lines represent the outline of cervix and adjacent tissues; the broken lines are the cervical canal; the heavy lines are the attached muscle, A and B representing muscle slips running down into the cervix. 1. Late pregnancy, before taking up of the cervix. 2. Cervix taken up (modified from Hughesdon, 1956).

formation of a recognisable 'lower segment'. Taking up (shortening) of the cervix and the start of cervical dilatation is a consequence of traction on the muscle bundles running down into it (Figure 1.1–1.2). If segments of human cervix are excised it is possible to detect areas, probably representing these muscle bands, which are capable of developing some 5 to 10 times the tension which the average segment of cervix, occupied by intrinsic muscle only, can produce (Hawkins, unpublished observations). The activity of such muscular extensions can easily account for the changes in shape of a softened cervix. As with formation of the lower segment, there is much variation in the time at which the cervix starts to change. In a small proportion of women the lower segment is already thinned at 32 weeks; Wood et al. (1965) show that 12% of women have a cervix which will admit a finger by 12 weeks. In some women, particularly primigravidae, these processes do not seem to start until labour is established.

Controversies over the nature of the functional processes which determine the structural changes that occur in the uterus have been a feature of the development of obstetric knowledge in this century. Most of the disagreements have provided the stimulus to objective studies which have resolved the problems and provided better understanding. It is clear that coordinated uterine contractions originate in the fundus, sometimes in the midline, sometimes in one or other cornual region. There is no harm in the term *pacemaker area*, provided it is understood that the area concerned is labile and diffuse. Moir in 1934 observed with the simplest methods that contraction in the fundus precedes that in the lower segment and cervix, and measured the amount of time taken for the contraction wave to travel from fundus to cervix as 17 seconds. Using sophisticated recording methods, with small balloons inserted surgically into the myometrium at various points, Alvarez and Caldeyro-Barcia (1954a) arrived at the conclusion that the contraction wave took between 10 and 20 seconds to traverse the uterus. There is no harm in the term *fundal dominance*, provided it is understood to indicate that contractions start in the fundus and travel down and that changes in their intensity reflect the mass of muscle concerned and the shape of the uterus at the point recorded. The term *coordinated* is useful, provided it is understood to mean contractions propagated in this way, tending to be regular in frequency, complete relaxation of the myometrium occurring after each wave, and having the functional capacity to thin the lower segment, take up and dilate the cervix, and eventually assist in the expulsion of its contents.

Disorders of uterine activity may be described in these terms. *Primary*, or *hypotonic*, uterine inertia is the consequence of an insufficiently mature or poorly stimulated uterus, developing insufficiently frequent, regular or powerful contractions to achieve progressive cervical dilatation. *Hypertonic inertia*, *incoordinate uterine action*, or *colicky uterus* are self-descriptive phrases and represent a situation where there is failure of the progression of regular correctly orientated contraction waves, creating a hypertonic situation with failure to achieve cervical dilatation. Constriction rings represent a special form of the failure of propagated contraction waves, sometimes a consequence of anatomical or functional abnormality of the myometrium, resulting in spasm of the uterus above the usual site of the lower segment, but generally in relation to prominent fetal structures inside. In the presence of powerful but incompletely propagated contractions they can lead to thinning and eventually rupture of the uterus. A contraction (Bandl's) ring developing at the junction of upper and lower segment represents the consequence of powerful well-orientated contractions overthinning the lower segment, either because of structural weakness or an unrecognised degree of disproportion. The thinning and

rupture of the uterus in prolonged obstructed labour take place at the same site.

If normal and abnormal uterine action are described in the above terms, such descriptions as 'hypertonic lower segment', 'functional cervical dystocia' or 'cervical spasm' cease to have meaning. The idea that the cervix has a will of its own has gradually been discarded, with the demonstrations that the muscle fibres in the cervix are functionally and pharmacologically identical with those in the rest of the uterus (Hawkins, 1961, 1964; Najak, Hillier and Karim, 1970), and that their special activity in dilating the cervix is solely a consequence of their anatomical disposition. The fact that the muscle of the cervix functions simply by transmitting and continuing the propagated contraction wave descending from the fundus was firmly established by Embrey and Siener's (1965) combined recordings of fundal and cervical activity in labour. These showed unequivocally that as the contraction wave reaches the cervix, it causes dilatation, the cervix relaxing partly or completely to its resting status between contractions. Lindgren and Smyth (1961) found only 3 cases which they could call true 'cervical dystocia', that is, failure of cervical dilatation with the normal forces of labour, in 23,000 primiparae. The term *cervical achalasia* should be reserved for the rare situation of congenital or acquired structural abnormality of the cervix caused by rigid fibrosis. 'Conglutination of the internal os' used to be a rare anatomical abnormality, but has become increasingly common as an aftermath of procedures to repair cervical incompetence or following cone biopsy.

The preceding descriptions of the uterus and its normal and abnormal function provide the basis for specification of the pharmacological activities of drugs on this organ, considered in terms of available methods of recording these activities. There have been attempts to demonstrate differential reactions to drugs of different layers of the uterus and of myometrium from different sites in the uterus. Such differences as have been found are, in the main, accounted for by variations in the amount and orientation of muscle in the excised segments of uterus studied, and in terms of variation found even between segments cut from adjacent sites. The balance of evidence at the present time is to the effect that myometrial cells from any site in the uterus are pharmacologically homogeneous and that functional differences depend on their anatomical disposition.

RECORDING OF UTERINE ACTIVITY

From what has been said of the anatomy and function of the pregnant uterus, it will be appreciated that the principal functional parameter of myometrial activity during pregnancy is intrauterine pressure, which gives a direct reflection of myometrial tone and contractions. For most purposes,

intraamniotic pressure is equivalent. In the first trimester, before the gestation sac fills the uterine cavity, extraamniotic pressure recordings are often appropriate; once the sac occupies the whole uterus, intraamniotic recordings give the best records of myometrial activity.

The use of these procedures is subject to clinical considerations. In early pregnancy, only short-term studies in patients having therapeutic abortion or similar operations are possible, as intrauterine manipulations at other times are likely to interfere with the course of the pregnancy and to introduce infection. In middle and late pregnancy similar considerations apply, though short studies can be conducted when amniocentesis is indicated for other reasons. It is reasonable to make intraamniotic recordings during the confinement, particularly if electrodes on the fetal scalp are also introduced to monitor the fetal heart. The information obtained on uterine and fetal activity is of sufficient clinical value to justify a small risk of intrauterine infection, though it may be deemed wise to provide antibiotic cover in the form of intramuscular benzylpenicillin (1 Mu 6-hourly) and streptomycin (1 g daily), or of cephaloridine (1 g 8-hourly).

Often it is necessary to have recourse to noninvasive monitoring techniques such as external tocography to record human uterine activity in pregnancy. There is no accurate way of calibrating the records, which are semiquantitative. Observations of drug activity made on isolated strips of myometrium obtained at hysterotomy or Caesarean section cannot be accepted as more than a basis for studies to be made in the intact human subject. There are many examples of drugs which fail to have the same action in vivo as in the isolated organ bath. Drug effects observed in nonpregnant women or in animal experiments are subject to the widest deviation from the responses of the intact human pregnant uterus. Extrapolation from these sources can only be taken seriously if it is in complete agreement with direct observations made in pregnant women.

Techniques are available for studying some specialised aspects of uterine action such as intramyometrial pressures (Alvarez and Caldeyro-Barcia, 1954a), 'head to cervix' pressures (Smyth, 1954; Lindgren, 1955; Lindgren and Smyth, 1961) and changes in the cervix (Embrey and Siener, 1965). They are of research interest, but in general merely confirm observations on drug action made by intrauterine pressure recording. The concept that the cervix has inherent activity and the capacity for independent response has died a natural death as familiarity with effective drugs acting on the myometrium as a whole has increased. It has become clear that cervical dilatation is a secondary consequence of coordinated myometrial activity in the *corpus uteri*, although undue rigidity or unusual softness of the cervix can moderate the process.

Internal Tocography

Early Pregnancy. Ethically reasonable opportunities for recording drug actions on the uterus may arise during procedures for therapeutic abortion. For example, patients may consent to brief observations of the effect of drugs which can aid contraction of the uterus and consequent haemostasis in relation to operative evacuation of the uterine contents. Also, the monitoring of uterine activity can be justified when pharmacological agents such as prostaglandins are used to effect abortion and for the study of drugs which may aid termination of the pregnancy after intraamniotic saline instillation.

The best recordings are obtained with a small thin-walled rubber balloon introduced through the cervix using aseptic and antiseptic precautions under general anaesthesia. Balloons as small as 5 mm diameter have been used and can be introduced without anaesthesia, but they are not so sensitive to pressure changes and are more susceptible to interference from contact with solid objects in the uterus. For short-term recordings under anaesthesia, the balloon is best inserted on a metal cannula of the type described by Schild, Fitzpatrick and Nixon (1951). For long-term monitoring relatively rigid plastic tubing is more suitable. If recordings sensitive to rapid fluctuations in pressure are required, the internal diameter of the system should not be less than 4 mm, but 2 mm tubing is adequate if this is not important. The system is filled with 0·9% saline containing the antiseptic detergent benzalkonium chloride, 1 in 5,000, and connected by tubing kept as short as possible to a pressure transducer, amplifier and chart recorder with a full scale range of up to 120 mmHg. If the balloon lies completely within the uterine cavity, recording is relatively efficient whether or not the gestation sac is intact.

In the former case slight distortion can occur because of the balloon lying with taut membranes on one side and uterine wall, which has some rigidity, on the other. If the membranes are ruptured the balloon can be distorted by contact with products of conception. Open-ended plastic catheters filled to the tip with antiseptic saline can be used, but there is often leakage back through the cervix and it is then necessary to maintain a very slow flow of saline through the catheter. This could in theory carry debris into open venous channels during the course of an abortion. Open-ended catheters have a tendency to lodge against uterine wall or products of conception and record tissue pressures rather than those in the cavity.

Whichever type of recording is employed there seems little necessity to obtrude the cervix completely. When the latter is relatively undilated the soft tissues fall together round the catheter. When the cervix is partly

dilated and the uterine contents are being expelled the intrauterine pressure reflects myometrial tension less accurately.

Late Pregnancy. At amniocentesis, a sterile plastic catheter may be connected to or introduced through the amniocentesis needle and left in situ for some hours if there is an indication for continued monitoring (Alvarez and Caldeyro, 1950; Reynolds, Harris and Kaiser, 1954a; Hendricks et al., 1959a; Cibils, Pose and Zuspan, 1962). Good amniotic fluid pressure records may be obtained in this way.

Labour. When accurate monitoring of uterine activity in labour is indicated, a saline-filled fine open-ended plastic catheter, introduced into the amniotic cavity either *per abdomen* or through the cervix when the membranes are ruptured, is superior to other recording methods. A very slow flow of saline tends to prevent blockage by contact with solid structures. Small balloons mounted on catheters can be introduced through the cervix, but the relative freedom from blockage they convey is counterbalanced by the increased risk of introducing infection, as they are larger and more difficult to sterilise.

Other Intrauterine Recording Devices. Volume or pressure recording with intrauterine bags is largely of historical interest—the bags are difficult to introduce and predispose to infection. It is seldom clear exactly what is being recorded. Moir (1936) introduced the use of recording of umbilical vein pressure as a reflection of intrauterine pressure in the third stage of labour—it may also be employed after the delivery of the first of twins. Karlson (1944) developed intrauterine pressure receptors depending on the electrical resistance of a capsule containing carbon granules. These can be placed between membranes and uterine wall with a probe and give a response related to myometrial activity, but are sensitive to contact with solid structures within the gestation sac. The bipolar electrodes inserted into the extraovular space described by Wolfs et al. (1971) seem to give a good record of uterine activity when labour is established, but require an electrical lead and offer no advantage over intraamniotic pressure recording. Little use has been made of the 'radio pill' (Watson, Ross and Kay, 1962) which can be introduced past the fetal head with a probe when the membranes are ruptured.

External Tocography

Mechanical Recording. Devices for recording activity of the pregnant uterus through the abdominal wall are adequate for many studies. The extent to which the records reflect tension in the uterine wall and intra-amniotic pressure varies from patient to patient with the thickness of the abdominal wall. The location of the recorder in relation to the uterus, the placenta (which tends to splint the uterine wall) and the fetal parts, also

affect the record (Embrey, 1958a). There is no simple way in which the intensity of a contraction can be calibrated, but qualitative observations on the pattern of activity, in conjunction with the measurements of frequency and duration of contractions, often provide all the information necessary. With a standard technique, good experimental design and statistical appraisal, quantitative comparisons of the activity of drugs can be made (Myerscough and Schild, 1955, 1958).

Basically, the Lóránd tocograph (Lóránd, 1936; Murphy, 1947) is simple, compact, self-contained, and of value for short-term recordings, but is uncomfortable for the patient to support for long periods in the supine position, particularly during labour. The original contention that the multiple receptors of the Reynolds 'multichannel strain-gauge tokodynamometer' (Reynolds et al., 1948; Reynolds, Harris and Kaiser, 1954b) could record fundal dominance in terms of a gradient of myometrial tension from fundus to lower segment has largely been abandoned. It is likely that the gradient represented merely the structures between the uterus and the receptors. Little use has been made of the instrument in recent years for studying the rate of progress of contraction waves from fundus to cervix—possibly because this is relatively unaffected by therapeutic agents. The Smyth 'guard-ring tocograph' (Smyth, 1954, 1957) is considered more comfortable for the patient but still produces the best results if the patient lies in the supine position—not the optimum posture for uterine action.

Interpretation of Records of Mechanical Activity. The parameters of uterine activity usually employed are the contraction pattern (Garrett, 1956, 1959; Sandberg et al., 1957) and measurements of resting tone and of rate and amplitude of contractions. Measurement of the integrated area under the record (Reynolds et al., 1954c), can be tedious, though electronic integrators are available (Styles and Sullivan, 1962). The Montevideo units employed by Caldeyro-Barcia et al. (1957), based on the product of amplitude and frequency of contractions, are of particular interest as they are a function of work done by the uterus.

For the assessment of responses to drugs, the basic requirement of the measurement is that it shall show a satisfactory dose-response relationship. The simplest parameter which satisfies this principle is often the most useful.

Electrical Recording. There is much work on the recording of uterine electrical activity with abdominal or vaginal electrodes (see Karlson, 1944; Reynolds et al., 1954d; Corey, McGaughey and Thornton, 1957; Steer, 1959; Larks, 1960). In the past this has not proved a profitable approach for studying the action of drugs. The records are difficult to interpret unless supplemented by observations of mechanical activity.