The Endocrinology of Parturition
The Endocrinology of Parturition

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Contents

VII Foreword
Grossman, A.B. (London)

IX Preface
Smith, R. (Newcastle)

1 The Socioeconomic Impact of Preterm Delivery
Gill, A. (Newcastle)

10 The Comparative Physiology of Parturition in Mammals
Young, I.R. (Clayton)

31 Prostaglandins and Uterine Activity
Patel, F.A.; Challis, J.R.G. (Toronto)

57 Oxytocin and Uterine Activity
Zingg, H.H. (Montreal)

66 Control of Intracellular Signalling by Corticotropin-Releasing Hormone in Human Myometrium
Hillhouse, E.W.; Grammatopoulos, D.K. (Coventry)

75 Role of the Human Fetal Adrenal Gland in the Initiation of Parturition
Jaffe, R.B. (San Francisco, Calif.)

86 Roles of Estrogen and Progesterone in Human Parturition
Mesiano, S. (New Lambton Heights)

105 Relaxin and the Cervix
Weiss, G.; Goldsmith, L.T. (Newark, N.J.)

113 Cytokines and the Initiation of Parturition
Rice, G.E. (Carlton)
147 Prostaglandins, the Fetal Membranes and the Cervix
Bennett, P.; Allport, V.; Loudon, J.; Elliott, C. (London)

165 Role of Mechanical Signals in the Onset of Term and Preterm Labor

179 Excitability in Uterine Smooth Muscle
Parkington, H.C.; Coleman, H.A. (Clayton)

201 Coordination of Myometrial Contractility
Young, R. (Charleston, N.C.)

216 The Placenta as a Neuroendocrine Organ
Reis, F.M.; Petraglia, F. (Siena)

229 Timing the Onset of Parturition
McLean, M. (Sydney)

246 Regulation of CRH Gene Expression in the Placenta
Nicholson, R.C.; King, B.R. (Newcastle)

258 Biochemical Predictors of Prematurity
Lockwood, C.J. (New York, N.Y.)

269 Metalloproteinases and Cervical Maturation
Giles, W.; Agrez, M. (Newcastle)

279 Pharmacotherapy for Preterm Labour
Cole, S.; Smith, R.; Bisits, A. (Newcastle)

308 Author Index

309 Subject Index
The smooth process of growth and development is interrupted by a single cataclysmic event which is also the most dangerous part of our lives – the moment of birth. Parturition is thus an event of exquisite importance in development, but paradoxically parturition has been surprisingly little studied. The evolutionary pressures on birth are tremendous, as errors in this process will severely compromise reproductive effectiveness. It is thus with great pleasure that we present the current volume in the *Frontiers of Hormone Research* series, where Roger Smith has brought together a host of international experts in the field of parturitional endocrinology. Roger is head of the Endocrine Unit at the John Hunter Unit in Newcastle, New South Wales, which he has established as one of the leading centres in researching this important and fascinating area. At the end of 2000 he hosted a Satellite Meeting of the International Society of Endocrinology in Australia, and many of the important contributions which we were privileged to hear at that time are included in this volume. As he points out in his Preface, the social, economic and personal impact of premature delivery is staggering, and only by understanding the biological process fully can we be in any position to intelligently interact with its pathological failure. This is an important area which hitherto has not been given the priority it deserves, and I hope that this volume, summarising much of the most important research in this area, will go some way to redressing the balance.

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Preface

Understanding the processes by which we ourselves are born is arguably the greatest current challenge in clinical medicine. Increasingly the intrauterine health of the baby is seen as a major predictor for adult disease. As healthcare costs spiral, the importance of delivering a healthy baby with a low likelihood of experiencing illness and able to fully engage in the activities of society becomes crucial. Further as family size plummets in Western counties, the significance of the health of, what is frequently, the only child in the family assumes massive proportions. In this socioeconomic setting our failure to be able to accurately predict and prevent preterm delivery, the cause of 70–80% of neonatal mortality and vast morbidity and associated healthcare costs, makes research in this area of key strategic importance. This book seeks to draw together the work of international experts on the endocrine processes of parturition and the prediction and treatment of premature labour.

In the 21st century in developed countries maternal mortality during pregnancy has become a rare and disastrous event, but the consequences of premature birth for the fetus remain substantial and the territory of the neonatologist. Dr Andrew Gill, a practicing neonatologist, outlines the social and economic burden of premature birth in the initial chapter. Failure to predict and prevent premature birth has driven neonatal care to evermore difficult territory as increasingly premature babies are maintained for increasing lengths of time in high-cost, high-tech environments with substantial economic cost to the community and immeasurable impacts upon the parents.

Why do we not understand the mechanisms of human parturition after centuries of diligent scientific research? A major difficulty in this area of research is the extraordinary variability in the processes of parturition observed amongst different mammals. An insight into this variability is provided by the chapter on mammalian reproduction by Ross Young. As David Haig [1] has cogently argued, mammalian pregnancy pits mother against fetus in a complex struggle. The fetus
must draw its nutrients from the mother and the more nutrients it draws the better it is able to grow and survive in the future, yet, if it draws too much nutrient from the mother the survival of the mother is threatened as is her ability to look after the newborn baby. From a maternal perspective there is a substantial investment in the fetus, however, if too much nutrient is provided to the fetus so that it adversely affects maternal health then the ability of the mother to create further offspring is threatened, placing her in the difficult position of providing enough nutrients to the baby but not too much. This complex interrelationship means that the fetus must constantly battle to achieve as much nutrient supply from the mother as possible while the mother must constantly adapt to limit this supply to optimise her chances of leaving progeny. This battleground has arguably produced a rapid rate of evolution and divergence leading to the many models for parturition currently observed amongst mammalia, where even species as closely related as goats and sheep have strikingly and apparently fundamental differences in their methods of inducing parturition. Pity the clinical investigator seeking a suitable animal model of human parturition.

Examination of comparative parturition in mammalia has identified many species where specific interventions can halt the process of parturition. The pioneering work of Mont Liggins in sheep dramatically illustrates this type of mechanism. Defects in the sheep fetal hypothalamus, pituitary or adrenal all permanently arrest the process of parturition in this species. Equally in mice, knockout of the COX-1 gene prevents parturition. These data argue strongly that the mechanisms of parturition in such species represent a linear sequential pathway. Intriguingly no such corollary exists in the human. There are no conditions and no described cases where the process of parturition is substantially interrupted. Fetuses with absent adrenals, pituitary and severely damaged hypothalami still deliver close to, or at, normal term; mothers with absent pituitaries and therefore no production of oxytocin still deliver their babies at term, and pregnancies characterised by massively disturbed oestrogen metabolism still deliver normally. These data argue strongly that the endocrine processes regulating parturition in the human do not consist of a single linear sequential pathway. It appears that in the evolutionary push and shove game of maternal/fetal interactions the human has evolved parallel pathways leading to parturition. They provide a failsafe signal that ensures delivery of the fetus. While the teleological benefits of such an approach can be argued, the scientific difficulties of investigating such a mechanism are substantial, especially when constrained by the obvious ethical difficulties associated with work in human pregnant women. The dual difficulties of lack of a suitable animal model and the likelihood of parallel pathways to parturition makes the elucidation of human parturition an exciting and challenging opportunity for researchers. The problem is being tackled on many fronts with many different techniques and strategies. The scientists involved bring many different skills to
the foray including electrophysiology, molecular biology, mathematical modelling and clinical epidemiology.

While there may be multiple pathways leading to parturition in the human many of the likely players have been identified. Prostaglandins are seen as a crucial and probably indispensable part of the activation of the uterus and digestion of the cervix in human parturition. John Challis is the international authority on this aspect of parturition and comprehensively covers current knowledge on this subject.

While oxytocin is used clinically to increase the force of uterine contractions especially following induced labour, pituitary oxytocin is clearly not essential for normal parturition in the human. Hans Zingg has demonstrated the presence of oxytocin within the endometrium and has shown novel interactions between progesterone and oxytocin receptors revolutionising our current thoughts on the role of this peptide in labour.

A relatively new player on the scene of human parturition is corticotrophin-releasing hormone produced by the placenta, yet with potential actions on the myometrium. Ed Hillhouse and Dimitri Grammatopoulos have produced the overwhelming majority of the current knowledge of this process. Their work suggests that corticotrophin-releasing hormone may well suppress uterine activity for the majority of pregnancy but key changes in its signalling pathway may herald the onset of parturition.

The classical steroid hormones of pregnancy, oestrogen and progesterone, have been shown to be crucial for the processes of parturition in many species, such as the sheep. While their role in human pregnancy is controversial, a further complexity is the unusual mechanism by which oestrogens are produced in primates from the fetal zone of the fetal adrenal cortex. Bob Jaffe’s lifetime work in this area has provided much of our current knowledge on these mechanisms and he describes the development and function of the fetal zone of the adrenal and his long-term collaborator, Sam Mesiano, follows with a discussion of current knowledge of oestrogen and progesterone in human pregnancy. The identification of multiple forms of 17ß-hydroxy steroid dehydrogenase able to metabolise inactive to active forms of oestrogen and vice versa and the identification of multiple oestrogen and progesterone receptors with profoundly different functions and expression have added a new level of complexity to our understanding of these classic steroids.

The role of relaxin produced in the ovary in human parturition also remains controversial but there is evidence that it may play a particular role in the increased pathologies observed following assisted reproduction when multiple ovulation is induced and circulating concentrations of relaxin are elevated. Gerson Weiss and Laura Goldsmith write authoritatively on the potential roles of relaxin in human parturition.
In the face of our ignorance of the mechanisms of human parturition new approaches must constantly be sought. In this setting the concept that parturition represents a variant of the inflammatory response is supported by an increasing volume of data. Greg Rice reviews information currently available on the role of the wide spectrum of known cytokines in parturition, and Phil Bennett extends this work particularly focussing on the potential role of the NFκB and its signalling pathway as potential activators of key genes in the pathways leading to labour.

Steve Lye has carefully explored the possibility that mechanical stretch of the uterus plays a significant role in the process of parturition. His physiological and molecular biological experiments have begun to elucidate a pathway within which physical stretch may directly influence the activity of the smooth muscle cells that form the uterus. Identification of these pathways may lead to new therapeutic targets. This work may explain the inevitability of parturition in the human.

The major target of the endocrine pathways leading to parturition is clearly the myometrial myocyte. To understand parturition the function of this cell and the mechanisms that determine its contractility must be clarified. This can be undertaken at the individual cell level and this approach is reviewed by Helena Parkington. Alternatively the function of the uterus at the whole organ level can be explored looking at the relationships between individual cells and how their activity can be coordinated to achieve effective uterine contractions. Effective modelling of uterine function has been reviewed by Roger Young.

Increasing evidence suggests that while parturition in the sheep may be determined by fetal events and parturition in murine pregnancy by maternal events, parturition in the human may well be controlled by the placenta. The placenta and its membranes are responsible for the production of oestrogen and progesterone, prostaglandins and many peptides specific to pregnancy. The endocrine function of the placenta is reviewed by Felice Petraglia and Fernando Reis. Work performed on placental endocrinology by Mark McLean and his coworkers have suggested a different paradigm for understanding human parturition. Mark’s work on placental production of corticotrophin-releasing hormone has suggested that the overall length of human pregnancy is determined close to the time of conception when a process is put in place that effectively times the future onset of delivery, a type of placental biological clock. This concept opens the way for the identification early in pregnancy of cohorts of women at high risk for the future onset of premature labour. While measurement of corticotrophin-releasing hormone itself lacks the sensitivity, specificity and positive predictive value to be clinically useful, it seems likely that measurement of a combination of analytes related to fetoplacental maturation may have the power to target antenatal care more effectively to the women most in need. Understanding placental biology will become increasingly important in this context and, in particular, understanding
the regulation of expression of genes such as corticotrophin-releasing hormone. Bruce King and Rick Nicholson describe current knowledge in this emerging area.

While identification of women at increased risk early on in pregnancy could be clinically useful, particularly for instituting preventative measures, it seems likely that many women will still present unexpectedly with the signs of preterm labour. This is a substantial clinical problem since over 50% of such women will not deliver prematurely, labour will spontaneously subside and they will deliver at term while the remainder experience the traumas and cost of preterm delivery. Clinically it has not been possible to distinguish which women in preterm labour will deliver promptly and which women will continue with their pregnancies until term. Increasingly biochemical and other markers are being sought to assist in this clinical conundrum. Charles Lockwood has been an international leader in this field of research and reviews currently available markers. A new marker, the metalloproteinase 9, has been identified in the urine of pregnant women and early work suggests that it has a high sensitivity and specificity in the prediction of preterm delivery and Warwick Giles reviews this exciting possibility.

As new basic science knowledge is accumulated on the mechanisms underlying human parturition, the clinical challenge is to incorporate this work into more effective treatments for women in preterm labour. Unfortunately currently available therapeutic agents have very poor efficacy with many women delivering prematurely in spite of the use of these treatments and, in addition, many carry unacceptable side effects such as the risk of fatal maternal pulmonary oedema with the use of β-sympathomimetics and substantial adverse effects on the fetus with the use of indomethacin. Steve Cole and coworkers review this problematic area providing suggestions on the methods that may be used to improve the effectiveness of trials of tocolytics and highlighting the potential need for combination therapy that targets more than one of the pathways leading to parturition.

In a field as dynamic as that of human parturition in the year 2000, producing a book that is timely and authoritative is, in itself, a challenge. I am grateful to the authors who responded so rapidly to the invitations to produce chapters and who have so successfully and ably summarised current knowledge in this difficult area. Each author is currently active in the field which they have reviewed and this is reflected in the authority of the writing. While it is inevitable that knowledge in this area will move on, it is equally inevitable that new knowledge and the development of new treatments, will be built on the foundations described by the authors of these chapters.

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Reference