Masterclass in Neuroendocrinology 15

Paula J. Brunton
David R. Grattan *Editors*

Neuroendocrine Regulation of Mammalian Pregnancy and Lactation

International Neuroendocrine Federation

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Masterclass in Neuroendocrinology

Volume 15

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Masterclass in Neuroendocrinology is published in collaboration with the International Neuroendocrine Federation (INF) https://www.inf-neuroendocrinology.org/. This series aims to illustrate and promote the use of the latest and most impactful technologies in basic and clinical research in the exciting field of neuroendocrinology. Neuroendocrinology is defined as the study of the control of endocrine function by the brain and the actions of hormones on the brain.

The series is made up of volumes that highlight different topics in neuroendocrinology that are of current interest and encompass the study of both normal and abnormal function, and the developmental origins of disease. They include the study of neural networks in the brain that regulate and form neuroendocrine systems, and also include the study of behaviours and mental states that are influenced or regulated by hormones. They also necessarily include the study of peripheral physiological systems that are regulated by neuroendocrine mechanisms. Some recent examples include: Developmental Neuroendocrinology, Neuroendocrine Clocks and Calendars, and Neuroanatomy of Neuroendocrine Systems.

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Series Preface

This series began as a joint venture between the International Neuroendocrine Federation and Wiley-Blackwell, and now is continuing with Springer Nature as publisher for the federation. The broad aim of the series is to provide established researchers, trainees, and students with authoritative, up-to-date accounts of the present state of knowledge, and prospects for the future, across a range of topics in the flourishing field of neuroendocrinology. The series is aimed at a wide audience as neuroendocrinology integrates the disciplines of neuroscience and endocrinology. We define neuroendocrinology as the study of how endocrine function is controlled by the brain and the actions of hormones on the brain. It encompasses the study of normal and abnormal function, and the developmental origins of disease. It includes investigation of the neural networks in the brain that regulate and form neuroendocrine systems, and also the study of behaviours and mental states that are influenced or regulated by hormones. In addition, neuroendocrinology encompasses the understanding and study of peripheral physiological systems that are regulated by neuroendocrine mechanisms. While neuroendocrinology embraces many issues of concern to human health and well-being, research in reductionist animal models is usually required to fully understand these issues.

Contemporary research in neuroendocrinology involves a wide range of techniques and technologies, from subcellular and systems to the whole-organism level. A particular aim of the series is to provide expert advice and discussion about experimental or technical protocols in neuroendocrinology research, and to further advance the field by giving information and advice about novel techniques, technologies, and interdisciplinary approaches.

To achieve our aims, each book focuses on a particular theme in neuroendocrinology. For each book we recruit editors, who are leaders in their field, to engage an international team of experts to contribute chapters in their individual areas of expertise. The mission of each contributor is to provide an update of current knowledge and recent discoveries, and to discuss new approaches, "gold-standard" protocols, translational possibilities, and future prospects. Authors are asked to write for a broad audience, to use references selectively, and to consider the use of video clips and explanatory text boxes; each chapter is peer-reviewed and has a glossary.

The masterclass series is open-ended; books in the series published to date are:

- *Neurophysiology of Neuroendocrine Neurons* (2014, ed. WE Armstrong & JG Tasker)
- *Neuroendocrinology of Stress* (2015, ed. JA Russell & MJ Shipston)
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- *Neuroendocrinology of Appetite* (2016, ed. SL Dickson & JG Mercer)
- *The GnRH Neuron and its Control* (2018, ed. AE Herbison & TM Plant)
- *Model Animals in Neuroendocrinology* (2019, ed. M Ludwig & G Levkowitz)

The first books of the series published by Springer Nature are:

- *Neurosecretion: Secretory Mechanisms* (2020, ed. JR Lemos & G Dayanithi)
- *Developmental Neuroendocrinology* (2020, ed. S Wray & S Blackshaw)
- *Neuroendocrine Clocks and Calendars* (2020, ed. FJP Ebling & HD Piggins)
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- *Neuroanatomy of Neuroendocrine Systems* (2022, ed. V Grinevich & A Dobolyi)
- *Neuroendocrine-Immune System Interactions* (2023, ed. JP Konsman & TM Reyes)
- *Cardiovascular Neuroendocrinology* (2023, ed, T Cunningham & G Yosten)

Under development are *Neuroendocrinology of Behavior and Emotions* (ed. H. K. Caldwell & H. E. Albers) and *Evolutionary and Comparative Neuroendocrinology* (ed. V Grinevich & R Oliveira).

Feedback and suggestions are welcome.

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Volume Preface

Pregnancy and lactation are remarkable physiological states where complex interactions between the nervous and endocrine systems lead to dramatic changes in a female's physiology. Several complex and interlinked adaptations emerge, driven primarily through the actions of hormones that serve to ensure a successful pregnancy outcome. The hormonal profile of mammalian pregnancy is distinctly different from the non-pregnant state. Some of these hormones (e.g. estrogen and progesterone) are familiar to female mammals, though the pattern of secretion changes and they are present at much greater levels than in the non-pregnant state, whereas others (e.g. human chorionic gonadotropin and placental lactogen) are seen for the first time during a first pregnancy.

Recently, there have been major advances in our understanding of the molecular mechanisms involved in regulating the neuroendocrine networks that govern mammalian pregnancy, parturition, lactation, and maternal behaviour. New technologies have enabled mapping of the neuronal circuits that control these maternal functions, imaging of their activity, and functional manipulation using genetic tools to establish how they operate. These adaptations are essential for pregnancy maintenance, optimal fetal growth and development, timely parturition, and the nourishment and care of the offspring postpartum. The neuroendocrine system plays a pivotal role in exquisitely coordinating these changes, and this is the focus of this book.

We begin with maternal recognition of pregnancy and the role of the placenta as an endocrine organ. In order for the hormone-induced changes in maternal physiology to be initiated, the blastocyst must signal its presence to the mother, in a process termed the maternal recognition of pregnancy (Chap. 1). Maintaining progesterone secretion by the corpus luteum is crucial to sustain pregnancy with species differences in the hormones providing luteotrophic support until the placenta develops. As pregnancy advances, the placenta becomes a prominent source of peptide and steroid hormones, which as well as supporting the pregnancy also act to prime the maternal brain in preparation for motherhood (Chap. 2).

Next follows a description of the adaptations in maternal neuroendocrine systems that are necessary for normal pregnancy, parturition, lactation, and maternal behaviour. There is a physiological shift in the brain regulatory networks controlling appetite and metabolism (Chap. 3) geared towards promoting increased food intake and energy storage. Increased energy intake in pregnancy not only supplies the growing uterus and placenta(e) but also supports the increased metabolic demands

of the mother and her developing fetus(es). In addition, the accumulation of surplus energy stores as fat facilitates milk production during lactation. Such adaptive changes, where the body is not responding to immediate requirements but rather is changing in preparation for future demands, are ideally suited to neuroendocrine control mechanisms. Hormonal signals can be used to predict the changes necessary in maternal physiology that will be necessary later to ensure a successful outcome. The hypothalamic–pituitary–adrenal (HPA) axis also undergoes adaptations to manage the increased metabolic demands of pregnancy and lactation and maternal stress responses are restrained to minimise exposure of the offspring to excessive levels of potentially damaging glucocorticoids (Chap. 4).

The transition from pregnancy to lactation and motherhood is another critical step facilitated by neuroendocrine mechanisms. The culmination of pregnancy and initiation of labour differs between species but in most mammals is triggered by a change in the balance of hormones produced by the mother, placenta, and fetus, in particular corticotropin-releasing hormone and glucocorticoids (Chap. 5). In late pregnancy, adaptations in the control of the neurohypophysial oxytocin system allow large stores of oxytocin to accumulate in the posterior pituitary gland to meet the demands of parturition and lactation. An increase in circulating estrogen sensitizes the uterus and mammary gland to oxytocin at the end of pregnancy. Hence, once labour is initiated, oxytocin augments myometrial contractions, promoting fetal expulsion (Chaps. 5 and 6), while postpartum, oxytocin plays an essential role in the milk ejection reflex in response to infant suckling (Chap. 6). Simultaneously, the neuroendocrine control of prolactin secretion shifts to permit a state of hyperprolactinemia during lactation, stimulating milk production to feed the offspring (Chap. 7). Following birth, new mothers display a dramatic change in behaviour. They care for their young, feed them, and protect them from environmental threats. The expression of these essential components of maternal behaviour is a consequence of hormonal priming of the neural circuits in late pregnancy in preparation for motherhood (Chap. 8).

Finally, the implications of these central adaptations for cognitive function and postpartum mood disorders are considered. Pregnancy effects on cognition are well recognised, with colloquial terms such as “mommy brain” or “pregnancy brain” commonly used in many societies. These terms often have a negative connotation, with mothers associating pregnancy with absent-mindedness or forgetfulness, but research actually shows improved performance in many cognitive tasks in pregnancy. The changes are perhaps better considered as natural, adaptive changes to the maternal brain that are prioritising a new infant-directed focus, and are necessary for expression of species-appropriate maternal behaviours (Chap. 9). Adaptations in maternal brain function in pregnancy and lactation, however, are evidently not without cost. Mental illness during pregnancy and the postpartum period is a growing public health concern and a societal and economic burden. The dramatic changes in neuroendocrine function during pregnancy and in particular the withdrawal of hormones postpartum have been proposed to contribute to perinatal mood disorders (Chap. 10).

The regulatory systems that adapt to support pregnancy covered in this volume are not an exhaustive list. Indeed, there are multiple other systems where neuroendocrine mechanisms are also known to play a critical role (Napso et al. 2018), such as altered cardiovascular control and osmoregulation which supports increased blood flow to the uterus and placenta ensuring a sufficient supply of oxygen and nutrients (Brunton et al. 2008; Russell and Brunton 2014). There is also evidence that pregnancy hormones influence adaptations in the regulation of other systems, including the sleep–wake cycle (Harrington et al. 2022; Irvine et al. 2023), thermoregulation (Grattan and Ladyman 2020), respiration (Bayliss and Millhorn 1992; Lomauro et al. 2019), the skeletal system (Winter et al. 2020), immune system (Motomura et al. 2023), and the gastrointestinal system and microbiome (Astbury et al. 2015; Yeo et al. 2022). Perhaps, once more research enables a fuller understanding of the neuroendocrine mechanisms involved in each of these processes, another volume will be justified!

This book is written for students, early career researchers, educators, and established researchers—anyone who is interested in understanding how the hormonal changes of pregnancy impact on the function of the maternal brain. The contributing authors are internationally recognised experts in the field. Together, the chapters in this book provide context for understanding the neuroendocrine adaptations in mammalian pregnancy and lactation. Research examples utilising both classic and cutting-edge approaches are employed to illustrate recent advances in the field, and areas where further research is needed are highlighted.

Understanding the neuroendocrine adaptations that occur during pregnancy and lactation is important. This is one of the most profound physiological challenges a women will face in her lifetime, and despite advances in medicine, there remain unacceptably high levels of complications. Comprehensive knowledge of the mechanisms that ensure optimal health of both the mother and her offspring can provide insights into potential therapeutic targets for pregnancy-related complications and disorders involving neuroendocrine dysregulation. As research in this field continues to advance, deeper insights into the complexities of these adaptations will pave the way for improved maternal and neonatal care.

Edinburgh, United Kingdom — Paula J. Brunton
Dunedin, New Zealand — David R. Grattan

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About the Editors

Paula J. Brunton is currently Senior Lecturer at the Centre for Discovery Brain Sciences, University of Edinburgh, UK. She received her bachelor's degree in Physiology in 1998 and her PhD in Neuroendocrinology in 2002, both from the University of Edinburgh. Her expertise lies in the area of stress neurobiology, neuroendocrinology, and behaviour. Her key research themes are focused on understanding the impact of maternal stress exposure during pregnancy on the mother, the pregnancy, her offspring, and subsequent generations, with a particular emphasis on unearthing the underlying central mechanisms involved and how the effects can be prevented or reversed. Her research has revealed the neuroendocrine mechanisms underlying altered stress responsivity in pregnancy and has also demonstrated that maternal exposure to stress during pregnancy is linked with adverse consequences for the offspring, some of which persist to the next generation. She has published over 60 peer-reviewed research articles, invited reviews, and book chapters, in the fields of neuroendocrinology and neuroscience. She has been Senior Editor for the *Journal of Neuroendocrinology* since 2017 and was elected to the Board of Trustees of the British Society for Neuroendocrinology in 2020. She organised the 4th International Parental Brain Conference in 2010 and continues to serve on the scientific advisory committee for this meeting. She is also actively involved in delivering taught undergraduate degree programmes in Biomedical Sciences at both the University of Edinburgh and Zhejiang University, China, on topics within the fields of endocrinology and neuroendocrinology.

David R. Grattan is Professor in the Department of Anatomy and was Director of the Centre for Neuroendocrinology at the University of Otago (2018–2023). He obtained a PhD in Physiology in 1991 from Victoria University of Wellington (New Zealand) and then held a post-doctoral fellowship at the University of Maryland School of Medicine (Baltimore, MD, USA), before returning to New Zealand to take up a Lecturer position in the Department of Anatomy at the University of Otago in 1995. He was promoted to full Professor in 2009, and served as the Head of this Department from 2011 to 2014. He has published over 150 research articles, invited reviews, and book chapters, in the fields of neuroendocrinology, endocrinology, and neuroscience, with a particular focus on the pituitary hormone prolactin and its role in the maternal brain during pregnancy and lactation. From 2009 to 2014, he was the

Editor-in-Chief of the *Journal of Neuroendocrinology*, and is currently Associate Editor for *Endocrinology*. He also chaired the organising committee for the 8th International Congress of Neuroendocrinology in Sydney, Australia, 2014. Dave has a strong interest in promoting the field of neuroendocrinology, the fascinating nexus between endocrinology and neuroscience.

Maternal Recognition of Pregnancy

1

David R. Grattan and Sharon R. Ladyman

Abstract

Hormone-induced adaptations occur in many aspects of maternal physiology during gestation. Before these changes can be initiated, the newly formed blastocyst must signal its presence to the mother. This process is known as the maternal recognition of pregnancy and occurs in all mammalian species, but there are important species differences in how this process is achieved. Because progesterone is essential to support uterine function in pregnancy, a critical step is to maintain the function of the corpus luteum, formed from the freshly ovulated follicle, to sustain progesterone secretion. Humans and other primates have an extended luteal phase during their menstrual cycle, and post ovulatory progesterone secretion continues for a period beyond the time of implantation. Hence, these species use a placenta-derived hormone, human chorionic gonadotropin, to act as a luteotrophic hormone. Commonly used laboratory rodent species, however, have a short luteal phase during their oestrous cycle, and progesterone secretion lasts for only a few hours after ovulation. These species use a mating-induced signal to support corpus luteum function to initiate pregnancy. A unique neuroendocrine reflex initiated by vagino-cervical stimulation during mating induces a pattern of twice-daily prolactin surges that provide luteotrophic support for the first part of pregnancy, maintaining progesterone secretion until implantation can occur. After formation of the placenta, placental lactogens take over as the primary luteotrophic hormones. This chapter reviews the initial pro-

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cesses whereby the establishment of pregnancy is signalled to the maternal endocrine system, sustaining progesterone secretion and enabling subsequent initiation of hormone-induced adaptive changes in maternal physiology and behaviour. In the interests of limiting the scope of the chapter, we have focused on humans and rodents, as the major biomedical research species. We have not attempted to describe the processes in the blastocyst and uterus leading to implantation, which are clearly important for pregnancy but do not have a significant neuroendocrine involvement. Similarly, we have not covered immune interactions between the conceptus and the mother.

Keywords

Human chorionic gonadotropin · Progesterone · Corpus luteum · Prolactin · Placenta · Placental lactogen · Pseudopregnancy

1.1 Introduction

The hormone-induced adaptations that occur in many aspects of maternal physiology during **gestation** are hallmark characteristics of the neuroendocrine response to pregnancy. The extended secretion of progesterone ("pro-gestation hormone") is essential for the initiation and maintenance of **pregnancy**. Therefore, before any other changes can be initiated, the developing **blastocyst** must signal its presence to the mother and maintain the corpus luteum in the ovary to prevent the loss of progesterone secretion that would normally occur at the end of each female reproductive cycle. This process is known as the "*maternal recognition of pregnancy*" and occurs in all mammalian species (Short 1969; Bazer 2015). There are important species differences, however, in how this process is achieved, due to marked differences in the normal duration of corpus luteum function and in mechanisms of **placentation**. In this chapter, we focus on two major examples: humans, as an example of a species with an extended **luteal phase** during its menstrual cycle; and the commonly used laboratory rodent species, which have a short luteal phase during their **oestrous cycle**, and therefore have evolved quite different mechanisms for the maternal recognition of pregnancy.

1.2 Critical Role of Progesterone for Pregnancy

For the duration of pregnancy, the developing **embryo/**foetus is exclusively dependent on the mother for its growth, nutrition, and protection. Indeed, many of the adaptations to maternal physiology described in this book can be viewed as the foetus subverting its mother's physiology to support its own development. Thus, maternal metabolism and glucose homeostasis are altered to provide nutrients to the foetus (see Chap. 3), and maternal immune function is altered to prevent rejection of the implanting embryo and to change inflammatory responses that might impair foetal development. Uterine and mammary tissues undergo marked changes to prepare for the future requirements of the foetus**/baby**. Cardiovascular and respiratory systems similarly change to optimize delivery of nutrients to the developing foetus. Moreover, both

pre- and post-partum behaviour is changed to encourage protection and nurturing of offspring, with nesting behaviour initiated during pregnancy, and complex maternal behaviours such as pup retrieval, nursing and maternal aggression initiated after birth to complement the process of lactation (see Chap. 8). All of these adaptations are driven by the hormonal changes that are associated with pregnancy. But the first and arguably most important hormonal change is the extended secretion of progesterone that starts in the luteal stage of the reproductive cycle and is then maintained for the duration of pregnancy. Progesterone is absolutely required for pregnancy.

The initial source of progesterone during pregnancy is from the corpus luteum that develops from the recently ovulated ovarian follicle, and then in some species, such as humans, the **placenta** of the developing embryo contributes essential progesterone in the latter parts of gestation. Progesterone is a steroid hormone, synthesized from cholesterol typically via a Δ^4-ketosteroid pathway (involving conversion to pregnenolone and then progesterone). It is secreted into the blood, where it circulates predominantly bound to steroid-binding proteins and albumin. It has a relatively short half-life in the body (around 5 min) and is predominantly metabolized in the liver by the enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase, with major metabolites including allopregnanolone and pregnanolone (Taraborrelli 2015). However, biologically significant metabolism also occurs in target tissues, including the brain, where functionally significant amounts of allopregnanolone can be produced from progesterone (Sundstrom-Poromaa et al. 2020). Interestingly, liver metabolism of progesterone means that oral progesterone absorbed via the hepatic portal vein is relatively ineffective at raising serum progesterone levels, an important consideration in the use of progesterone as a therapeutic or contraceptive compound. This has resulted in the development of alternative formulations (e.g., micronized progesterone, (Fitzpatrick and Good 1999)) or the use of synthetic progestins in oral treatments that might have different biological properties compared with natural progesterone (Pletzer et al. 2023). Progesterone acts via two related isoforms of the progesterone receptor, the full-length PRb and the truncated version, PRa (DeMayo and Lydon 2020), and by membrane receptors (progesterone receptor membrane component, PGRMC1 and 2) and membrane-associated kinases. In addition, its metabolites, such as allopregnanolone, can have important neuronal actions by positive allosteric modulation of $GABA_A$ receptors on neurons.

In the initial stages of pregnancy, progesterone has a critical role in preparing the uterine endometrium for **implantation** of the blastocyst (see Box 1.1). It promotes the transition of the endometrium from the oestradiol-dependent proliferative phase prior to the time of ovulation, in which re-epithelialization, stromal proliferation, and angiogenesis occur, to the secretory phase, in which the endometrium transforms into a form suitable for implantation, driven by increased levels of progesterone from the post-ovulatory corpus luteum. It is also critical for the **decidualization** response, where fibroblastic stromal cells underlying the endometrium undergo localized proliferation and transformation to become endothelioid cells, enabling trophoblastic cells of the blastocyst to invade and establish the early placenta. Early progesterone receptor (PR)-knockout studies showed that classical PR-mediated nuclear signalling in the uterus was necessary for decidualization and implantation (Lydon et al. 1995; Mulac-Jericevic et al. 2000). Once pregnancy is established, progesterone promotes

immunotolerance, and stimulates the growth and vascularity of the uterus to support foetal and placental growth. It also suppresses myometrial contractility and helps maintain cervical integrity, promoting a suitable uterine environment for appropriate foetal growth and development. Loss of progesterone at any time during pregnancy will cause termination of the pregnancy, and hence the progesterone receptor antagonist RU486 (mifepristone) has been used as a drug to induce abortion. Mechanisms to maintain progesterone secretion are a common feature of diverse, species-specific processes to enable maternal recognition of pregnancy.

Box 1.1: Miscarriage

Georgeanna Seegar Jones (1912–2005), the director of the Johns Hopkins' Laboratory of Reproductive Physiology in the mid-1900s, first described luteal-phase deficiency as a primary cause of infertility and pregnancy loss due to inadequate endometrium preparation and support (Jones 1949). She was credited with being the first person to use progesterone to treat women with a history of miscarriages (Damewood and Rock 2005; Di Renzo et al. 2020). It is estimated that natural conception in humans is only 30% per cycle (Zinaman et al. 1996), with early pregnancy loss (prior to clinical detection) common due to implantation failure, and up to 50–60% of all conceptions failing to advance beyond 20 weeks of gestation (Norwitz et al. 2001). Miscarriage, or spontaneous loss of clinically established pregnancy, is also common, affecting up to 15% of pregnancies (Devall and Coomarasamy 2020). A proportion of these pregnancy losses is attributed to a non-responsive endometrium caused by a lack of progesterone action (Zhang et al. 2013). The corpus luteum is supported by luteinizing hormone driven by pulsatile secretion of gonadotropin-releasing hormone (GnRH) (Mesen and Young 2015), and there is some evidence that luteal phase deficiency may result from impaired neuroendocrine support of the corpus luteum leading to impaired progesterone production (Soules et al. 1989). Classic experiments in rhesus monkeys demonstrated a key role for ongoing luteotrophic support by pulsatile GnRH and LH throughout the luteal phase (Hutchison and Zeleznik 1984). A remarkable recent study found that around a third of women of European descent express a variant of the progesterone receptor that originates from the Neanderthal genome (Zeberg et al. 2020). This is around ten times more prevalent than other Neanderthal gene variants found in modern humans, suggesting it provides a favourable effect on fertility. The study found that women with this receptor variant produced more progesterone receptors in their endometrial cells, tended to have fewer miscarriages, and more live births (Zeberg et al. 2020). The role of progesterone in supporting early pregnancy is unequivocal (Mesen and Young 2015), but 70 years after Seegar Jones' discovery, it remains debated as to whether supplementation of progesterone is an effective treatment for miscarriage (Devall and Coomarasamy 2020), perhaps because an impaired response to progesterone may also contribute to luteal phase deficiency. More research is required to understand this critical process.

1.2.1 Suppression of Concurrent Pregnancy

One key function that occurs during early pregnancy in most mammals is the suppression of fertility to prevent concurrent pregnancies. While there are a few mammalian species that have evolved a superfetation strategy (sequential fertilization of oocytes from multiple ovarian cycles), including European Badgers, Brown Hares, and American Mink (Roellig et al. 2010; Roellig et al. 2011), in most species there is no further ovulation once pregnancy is initiated. This focuses maternal resources towards supporting the growing foetus and towards preparation for lactation (see Chap. 3). It is highly likely that the high progesterone levels characteristic of early pregnancy will suppress ovulatory activity, as progesterone is known to profoundly inhibit activity of the kisspeptin neurons required for normal follicular development (McQuillan et al. 2019). Interestingly, it seems that waves of follicular activity continue to occur during pregnancy (Kirillova et al. 2021), presumably representing the gonadotropin-independent phases of follicular development. In the presence of high progesterone, however, gonadotropin secretion is low, and so follicles are not selected and stimulated through the gonadotropin-sensitive growth phases required to develop into large antral follicles and subsequent ovulation. In rodents, the mating-induced prolactin surges may also contribute to the suppression of pulsatile LH secretion and consequent fertility. Prolactin is known to have an inhibitory action on LH secretion, acting through direct inhibition of hypothalamic kisspeptin neurons (Brown et al. 2014, 2019; Hackwell et al. 2023).

1.3 Establishment of Human Pregnancy

1.3.1 Human Chorionic Gonadotropin

In humans (and other primates), a spontaneous luteal phase occurs after ovulation, with progesterone secretion from the newly developed corpus luteum peaking approximately 7–8 days after the preovulatory luteinizing hormone (LH) surge and subsequent ovulation. This peak coincides with the 2-day endometrial window when a blastocyst can attach to the endometrial surface. In the absence of fertilization, luteal support from the LH surge is lost and **luteolysis** will occur a few days later, leading to a fall in progesterone and the onset of menstruation. If fertilization has occurred, the blastocyst will implant in this time-window approximately 7–9 days after ovulation. Human chorionic gonadotropin (hCG) is synthesized in the **syncytiotrophoblast** of the implanting blastocyst as early as 6–7 days after fertilization, and will immediately pass into the maternal circulation as soon as the blastocyst embeds in the uterine endothelium. Therefore, hCG is present in the maternal circulation as soon as implantation occurs, and prior to the normal time of luteolysis in the menstrual cycle (Gridelet et al. 2020). hCG binds to LH receptors in the corpus luteum to support luteal function and prevent luteolysis, and therefore provides the key signal enabling maternal recognition that pregnancy has been initiated (see Fig. 1.1). Administration of exogenous hCG will prolong luteal function and

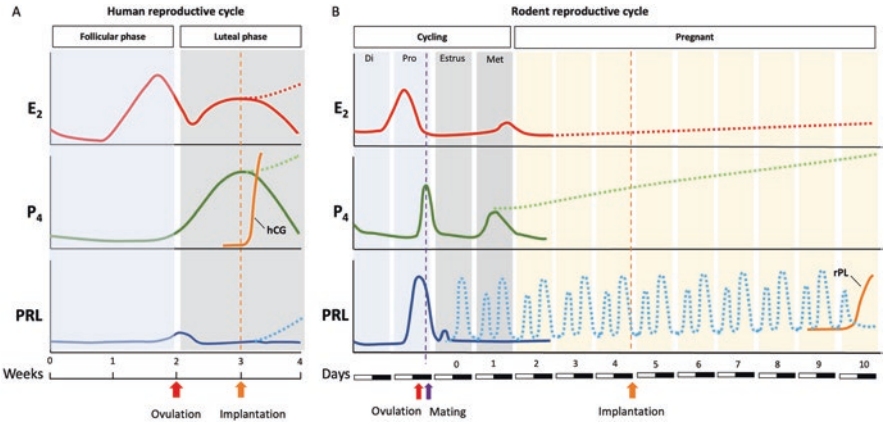

Fig. 1.1 Hormone changes in early pregnancy. Diagrammatic representation of hormonal changes in early pregnancy comparing (**a**) human and (**b**) rodent (modified from Phillipps et al. 2020). Note the similarities in the pattern of oestradiol (E_2; red line), progesterone (P_4; green line), and prolactin (blue line) during the follicular phase (preceding ovulation; blue shaded region; Di: dioestrus, Pro: **proestrus**) and early luteal phase (grey shaded region; Oestrus and Met: **metestrus**). The solid lines represent hormone levels in the reproductive cycle, with the dotted lines representing the changes in secretion that accompany pregnancy. In humans, implantation of the blastocyst leads to rapid production of human chorionic gonadotropin (orange), signalling the presence of the embryo to the maternal system and sustaining progesterone production. In rodents, however, the luteal phase is very short (<2 days), meaning that progesterone secretion would not last until the time of implantation (orange dotted line) on day 4–5 of pregnancy. Hence, mating induces a pattern of twice-daily prolactin surges that provides luteotrophic support to maintain progesterone secretion from the corpus luteum and sustain pregnancy (pale yellow-shaded regions represent the extended luteal phase in the presence of luteotrophic support from prolactin). Typically, rodents show a prolonged period of dioestrus-like vaginal smears during pregnancy, dominated by leukocytes with increasing levels of mucous present. After implantation and formation of the placenta (around days 8–10 gestation), placental lactogen (rPL) secretion becomes the primary luteotrophic support, and results in termination of the prolactin surges by negative feedback to the hypothalamus and pituitary gland

increase progesterone secretion in non-pregnant women. Conversely, passive immunization against hCG in marmosets neutralized chorionic gonadotropin function and prevented rescue of the corpus luteum, resulting in the prevention of pregnancy. Similar data have been achieved with immunization against hCG in women (Talwar 1999). These data suggest that hCG is both necessary and sufficient for the prevention of luteal regression in primates.

hCG was conceptually discovered almost 100 years ago, with the demonstration by Ascheim and Zondek that the blood and urine of pregnant women contained a "gonad-stimulating substance" (Lunenfeld 2004; d'Hauterive et al. 2022). It is a glycoprotein hormone composed of two subunits, closely related to the pituitary gonadotropins. It has a relatively long half-life in blood (24–36 h) and about 20% is excreted in urine. This characteristic of hCG has been capitalized upon to establish simple pregnancy testing in humans (see Box 1.2). Apart from its critical action to support the corpus luteum and stimulate progesterone secretion in early pregnancy,

hCG may exert other actions through the LH receptors. In particular, hCG binds to its receptor in the decidua, promoting the secretion of factors such as prolactin and leukaemia inhibitory factor and decreasing secretion of interleukin-6, factors that influence embryo implantation (d'Hauterive et al. 2022). It also supports angiogenesis within the uterine endothelium (Gridelet et al. 2020). Interestingly, LH receptors have also been found in the brain (Ryu et al. 2022), leading to speculation that hCG could influence neuronal activity in the mother during pregnancy. For example, it has been suggested that elevated hCG acting on LH receptors in the brainstem may explain the nausea and vomiting that occurs in some women during normal pregnancy (Cole 2010). However, despite the extremely high levels present in the blood, there is little evidence that hCG crosses the blood-brain barrier and has a significant "neuroendocrine" function in the maternal brain.

Box 1.2: Pregnancy Test

The most common self-administered pregnancy test currently used is a lateral flow test for human chorionic gonadotropin (hCG) in urine. The image shows an example of a positive pregnancy test. hCG is released from the developing conceptus in high amounts very soon after implantation (see also Fig. 1.1), and 20% of hCG is excreted in urine. Thus, hCG can be detected in urine as early as 8 days after conception (even a few days before an expected menstrual period) (d'Hauterive et al. 2022). Because of the convention that human pregnancy is dated from the time of the last menstruation, a positive test at the time of a missed menstrual period will be counted as 4 weeks pregnant (with weeks 1 and 2 actually occurring prior to ovulation!).

The history of using hCG as a pregnancy test is fascinating, with multiple different bioassays developed. Prior to the 1920s there was no definitive test to determine pregnancy, except waiting for the onset of morning sickness, breast tenderness, weight gain, or even the first movements of the foetus to confirm any external examination that was undertaken. There is recorded

(continued)

Box 1.2 (continued)
evidence that ancient Egyptians had a "pee-based" test whereby the curious woman would urinate on barley and wheat plants, then growth of the plants would indicate a pregnancy, and which plant grew would indicate the sex of the baby. While there is no evidence of the latter being correct, a study to recreate this test has shown that it is about 70% accurate in positively revealing a pregnancy with the high oestrogen levels in the urine thought to underlie the growth in the plants (Ghalioungui et al. 1963). In the 1920s, Berlin-based gynaecologists Selmar Aschheim and Bernhard Zondek demonstrated that urine from pregnant women contained a substance that promoted development and growth of the ovary (Finkel 1931). This study involved twice-daily injections of urine from a pregnant woman into pre-pubertal female mice. This led to the development of the so-called "A-Z test", in which the urine from a woman could be tested to confirm pregnancy as little as 2 weeks after implantation. This test was time-consuming, however, as it needed to be done in a specialized laboratory and required twice-daily injections into at least five mice that were all killed at the end of the test for dissection and analysis of the uterus and ovary. Not long after they developed the "A-Z test", Ascheim and Zondek's research ended abruptly when these men, both Jewish, were forced to flee Nazi Germany. By then, however, American doctor Maurice Friedman had adapted the test in the United States using rabbits, leading to the colloquial phrase "the rabbit died" to indicate a pregnancy (in actual fact though, the rabbit would die whatever the outcome of the test) (Kelley 2010). Subsequently, in the 1930s, British scientist Lancelot Hogben, while working in South Africa, injected a local type of frog, the *Xenopus laevis*, with urine from a pregnant woman and noticed that this rapidly triggered the appearance of a clutch of eggs on the frog's back. The fact that frogs did not need to be killed to get the results and the reduced time to get the results (less than 24 h after urine administration) made the frog a superior animal bioassay, and it became the popular choice for pregnancy testing. *Xenopus laevis* were exported around the world for this purpose. In 1947, it was demonstrated that urine from pregnant women was able to induce the detachment of spermatozoa from the Sertoli cells in the testis of toads, similar to the action of toad gonadotrophins from the pituitary, leading to yet another animal-based bioassay. In this test, the presence or absence of spermatozoa in the toad urine just hours after the injection of urine from the suspected pregnant women was assessed, with the presence of spermatozoa indicating a positive test result (Galli Manini 1947). Remarkably, while these animal-based tests that relied on the presence of hCG in the urine for the positive test began to be used from 1927, the hormone itself was not actually isolated until the 1950s (Kelley 2010). The advent of antibodies to detect hCG and the testing process refined over time to an easy "pee on a stick" protocol, means a laboratory and animal-based bioassay approaches are no longer required. The history of pregnancy tests in the 1900s, however, illustrates how scientific knowledge can be used and applied even if all of the details are not yet fully understood.

The production of a chorionic gonadotropin that is required to sustain progesterone secretion during pregnancy is largely restricted to primates. Horses have an equivalent chorionic gonadotropin, but in many other species with a long luteal phase, such as sheep, cows, and pigs, such a hormone is not produced. Corpus luteum function is controlled by a balance between luteotrophic factors, such as LH from the maternal pituitary gland, and luteolytic factors that promote degradation of the corpus luteum (Bazer 2015). In these species, pituitary luteal support from LH seems to be sufficient to sustain the corpus luteum indefinitely, and termination of the reproductive cycle is achieved through a luteolytic signal (prostaglandin F2α) from the uterus. Following implantation, pregnancy-specific factors in the implantation site (trophoblast interferon) suppress local prostaglandin production and prevent the induction of luteolysis (Arosh et al. 2016). Functionally, this provides that same outcome, maternal recognition of pregnancy and maintenance of luteal progesterone secretion.

1.3.2 Other Placental Hormones

In women, the corpus luteum remains the primary source of progesterone to maintain pregnancy for around the first 6–9 weeks of gestation, after which the placenta becomes the primary source of progesterone for the remainder of the pregnancy (Costa 2016). The placenta is also a primary source of oestrogens in pregnancy, together with the somatomammotropins, a class of protein hormones related to growth hormone (human growth hormone variant; hGH-V) and prolactin (human placental lactogen, hPL; also known as chorionic somatomammotropin). Hence, by the end of the first **trimester**, the human conceptus is largely self-sufficient in its endocrine requirements, and, indeed, is signalling through both steroid and peptide hormones to influence maternal physiology (see Chap. 2). In many other species, the placenta does not produce sufficient levels of steroid hormones, and there remains a dependence on ovarian luteal progesterone to maintain the pregnancy. In those species (e.g., rodents, pigs, cows), removal of either the pituitary gland or ovaries will lead to a loss of progesterone in the blood and termination of the pregnancy.

1.4 Maternal Recognition of Pregnancy in Species with a Short Luteal Phase

1.4.1 Mating-Induced Signals for Maternal Recognition of Pregnancy

The primary biomedical research animals are rodents such as rats and mice, and in many ways, they provide excellent models for the study of pregnancy biology. However, it is important to be aware of key differences and take these into consideration in experimental design. Unlike humans, who experience a luteal phase of the

menstrual cycle lasting 7–10 days, rodents have a short oestrous cycle with a particularly truncated luteal phase (metestrus) that only lasts a few hours (Freeman 1994). This means there is insufficient time for implantation to occur and maternal recognition of pregnancy to be established before the normal time of luteolysis and loss of progesterone secretion (see Fig. 1.1). Because of their size and relative ease of collecting blood samples, most work to date has characterized hormone levels in the rat (Freeman 1994). A recent study monitored hormone levels throughout the oestrous cycle in mice (Wall et al. 2023), showing some similarities with the rat and some specific differences, most notably an earlier peak in oestradiol levels. Nevertheless, the very short luteal phase was confirmed in that study. In the absence of a placental signal, rodents have evolved to use mating as a surrogate marker of pregnancy. Mating induces a pattern of twice-daily surges of prolactin secretion from the female pituitary gland (Gunnet and Freeman 1983), and this prolactin is the predominant luteotrophic hormone maintaining progesterone secretion during the first week of gestation (prompting some people to use the alternative name of "luteotropin" or "luteotrophic hormone" for prolactin (White 1949)). From around day 7–8 of gestation, placental lactogen becomes detectable in the maternal blood, with both rats and mice having two separate placental lactogens (PL) produced by the placental trophoblast cells: PL-1, peaking around mid-pregnancy, and PL-2, increasing from mid-pregnancy to peak around day 14, then remaining high until parturition (Voogt et al. 1982; Tonkowicz and Voogt 1983) (see Fig. 4.3 in Chap. 4).

In addition to placental lactogens, the decidualized stromal cells of the uterus also produce prolactin and other factors belonging to the prolactin family of hormones (e.g., Prl8a2, and Prlr3c1), and these are thought to contribute to supporting the implanting blastocyst (Prigent-Tessier et al. 1999). For example, decidual Prl8a2 is induced by Notch signalling in the uterus, and this appears to contribute to sustaining corpus luteum function in mice through the mid-pregnancy period when luteotrophic support is transitioning from pituitary prolactin to placental lactogen (Bao et al. 2021). This prolactin variant, however, does not act through the prolactin receptor (Rasmussen et al. 1996), and so its luteotrophic action must be independent of that of pituitary prolactin. Decidual prolactins are insufficient to sustain luteal function in the absence of pituitary prolactin, and thus, may have other functions. This is supported by the observation that progesterone replacement does not completely prevent pregnancy loss in prolactin- or prolactin receptor-knockout mice (Binart et al. 2000; Vomachka et al. 2000), suggesting that prolactin may act to support embryo survival distinct from its luteotrophic action. It is likely that decidual prolactin or prolactin-like hormones may mediate this function. For example, decidual prolactin has been shown to suppress the expression of several factors that contribute to foetal loss, including inflammatory cytokines (Bao et al. 2007; Alam et al. 2015). In women, an absence of decidual prolactin has been associated with first trimester miscarriage and with upregulation of these inflammatory cytokines (Garzia et al. 2013).

Interestingly, the rise in placental lactogen from mid-pregnancy in rodents leads to the inhibition of the mating-induced prolactin surges, as these placental lactogens bind to the same receptors as pituitary prolactin and therefore activate the dopamine-mediated negative feedback system to block prolactin secretion (see Chap. 7). Thus, placental lactogen production effectively establishes a condition of hyperprolactinemia during pregnancy, bypassing the maternal regulatory mechanisms that would normally suppress prolactin secretion.

1.4.2 A "Unique Neuroendocrine Response"

The pattern of prolactin secretion following mating has been best characterized in rats, and was aptly described as a "unique neuroendocrine response" (Gunnet and Freeman 1983). What makes this particularly unusual is that it is induced by a single stimulus, mating, but then manifests as a **circadian** pattern of prolactin secretion characterized by twice-daily surges of prolactin that repeat over many days, apparently invoking some sort of memory of the mating stimulus. There have been multiple studies evaluating what it is about the mating stimulus that establishes and sustains such a long-lasting pattern of secretion. It is initiated by the vagino-cervical stimulation that occurs during coitus, and can be replicated artificially by mechanical or electrical stimulation of the cervix. Thus, it does not appear to require specific behavioural or pheromonal interactions with the males. Nevertheless, the quality of the signal can be altered by specific female sexual behaviours, and is most robust if the female can control the pacing of interactions with males and, therefore, the timing of the stimulation that is received (Frye and Erskine 1990; Erskine 1995).

Female reproductive behaviour will normally only occur in a specific period of behavioural oestrus driven by the presence of sufficiently high levels of oestrogen and progesterone. These ovarian steroids are produced by the developing preovulatory ovarian follicle and peak at a time associated with ovulation. Thus, females will only engage in mating at a time that coincides with ovulation, maximizing the opportunity for fertile pregnancy to result from each mating. The mating-induced luteotrophic response is therefore also optimally timed to occur when a post ovulatory corpus luteum is forming, providing maternal recognition of pregnancy by rescuing and maintaining ovarian progesterone production. The same ovarian steroid hormone signal that drives ovulation and reproductive behaviour primes the neuroendocrine circuits to establish the mating-induced prolactin surges (Gunnet and Freeman 1983). Indeed, even in the absence of mating, elevated levels of oestrogen and progesterone can induce prolactin surges and cause **pseudopregnancy**-like changes in the oestrous cycle (de Greef and Zeilmaker 1979). Similarly, stress may induce prolactin secretion, and under the appropriate conditions, can result in a self-sustaining pseudopregnancy. These observations provide some insight into the mechanisms driving the prolactin surges (see below).

Box 1.3: Pregnancy Block, or the "Bruce Effect"
Because maternal recognition of pregnancy in rodents is regulated by a neuroendocrine pathway, it is possible for exogenous factors such as pheromones or stress to impact on the successful maintenance of the pregnancy. The "Bruce effect", named after the person who first described it (Bruce 1959), is a condition of pheromone-induced pregnancy failure when a pregnant female mouse is exposed to an unfamiliar male mouse (usually of a different strain to the male that mated with her to induce the pregnancy). The key mechanism is a neuroendocrine pathway, mediated by a pheromone-induced increase in dopamine production from the **tuberoinfundibular dopamine (TIDA) neurons** (Rosser et al. 1989), blocking the prolactin surges of early pregnancy and thereby removing luteotrophic support. As mice are completely dependent on luteal progesterone to support the pregnancy, this results in abortion. The pheromone involved is exocrine gland-secreting peptide 1 (ESP1), which is produced in tear fluid of adult male mice and is detected by the specific receptor V2Rp5 in the vomeronasal sensory neurons of the female. Pregnancy is terminated due to a failure of luteal function, and this can be mimicked by exposure to exogenous ESP1 (Hattori et al. 2017). From an evolutionary perspective, it is assumed that the Bruce effect may have a reproductive advantage of avoiding infanticide by unmated males, with the new dominant male contributing to parenting of his own pups (Elwood and Kennedy 1990).

The fact that vagino-cervical stimulation in rats caused oestrous cycles to cease was first described over 80 years ago by Greep and Hisaw, who describe how this induced a period of pseudopregnancy characterized by persistent dioestrus-like vaginal smears (Greep and Hisaw 1938). With the development of radioimmunoassays enabling measurement of pituitary hormones in blood in the 1970s, Smith, Freeman, and colleagues provided comprehensive descriptions of the patterns of hormones associated with these changes, particularly identifying the role of elevated prolactin in sustaining progesterone secretion after mating (Smith et al. 1975). They described the twice-daily surges of prolactin, referring to them as a diurnal surge (peaking in the afternoon towards the end of the light period) and a nocturnal surge (peaking late in the dark period) (Gunnet and Freeman 1983). Female sex behaviour establishes sufficient vagino-cervical stimulation to maximize the signal initiating these surges, with a threshold level of stimulation establishing an "all or none" neuroendocrine response, the magnitude of which is not altered by additional stimulation (Erskine 1995). Prolactin surges are more likely to be generated by multiple intromissions (>5), particularly if those are spaced apart. If allowed to control interactions with the male, the female will establish these conditions to optimize the luteotrophic response. The **lordosis** response, part of normal female reproductive behaviour, is required to enable intromissions, but is insufficient by itself to stimulate the prolactin surges (Erskine 1995).

Interestingly, because there is no requirement for a placental signal, pregnancy-like hormonal changes can occur in the absence of fertilization, such as after artificial stimulation or mating with a vasectomized or infertile male. This condition, known as *pseudopregnancy*, is characterized in rats by identical patterns of twice daily prolactin surges from the female pituitary gland and sustained progesterone secretion from the corpus luteum, as normally seen in pregnancy (Gunnet and Freeman 1983). In the absence of placental lactogens from a fertile pregnancy, this pattern of secretion will persist for even longer than that seen in pregnancy (where the initiation of placental lactogen secretion terminates the maternal prolactin surges by negative feedback). The eventual termination appears to be driven by luteolytic factors from the uterus that inhibit progesterone secretion and block prolactin release from the pituitary gland (Freeman 1979; Gorospe et al. 1981). While not as well-characterized as in rats, mouse pregnancy is also dependent on mating-induced prolactin. Some studies have observed twice-daily surges of prolactin, as seen in rats (Larsen and Grattan 2010), but others report only a single daily surge during the light phase (Yang et al. 2009). These differences may be due to strain or housing conditions, or differential timing of the prolactin surges.

1.4.3 Neuroendocrine Regulation of the Mating-Induced Prolactin Surges

The circadian pattern of prolactin secretion induced by mating involves interactions between the hypothalamus and pituitary lactotrophs. As mentioned above, the same pattern can be triggered by exogenous steroid hormones (de Greef and Zeilmaker 1979), but will also occur in ovariectomized rats, demonstrating that the ovarian steroids are not essential for expression of these surges. Similarly, this pattern of prolactin surges can be induced by central injections of prolactin itself (Helena et al. 2009), or a prolactin-releasing factor such as oxytocin (Kennett and McKee 2012). These observations facilitated a mathematical model that predicted such a pattern could essentially be generated by the normal negative feedback pathways that control prolactin secretion (Bertram et al. 2006; Egli et al. 2006). In this model, a rise in prolactin induced by mating (or any other stimulus) will, after a delay, trigger a compensatory activation of the tuberoinfundibular dopamine (TIDA) neurons that inhibit prolactin secretion (see Chap. 7). Elevated dopamine will subsequently suppress prolactin secretion, but then the falling prolactin will lead to a reduction in TIDA neuronal activity and a fall in dopamine release, thereby allowing a rebound rise in prolactin secretion. The self-sustaining rise and fall in prolactin secretion seems to be facilitated and entrained to the circadian cycle by the involvement of an endogenous rhythm that stimulates prolactin secretion at particular times of day (Arey et al. 1989). While normally masked by the inhibitory tone coming from the TIDA neurons, when unmasked by a reduction in TIDA neuronal activity, this will promote prolactin secretion at particular phases of the circadian cycle.

In the case of mating, it is proposed that a mating-induced release of oxytocin acts as a prolactin-releasing factor at the pituitary gland to provide the initial

stimulus to prolactin secretion (Kennett and McKee 2012). This is because lactotrophs express the oxytocin receptor (Breton et al. 1995), and administration of an oxytocin receptor antagonist at the time of cervical stimulation will block the induction of the subsequent prolactin surges (McKee et al. 2007). The circadian element involved in controlling the mating-induced prolactin surges appears to involve vasoactive intestinal peptide (VIP) neurons in the suprachiasmatic nucleus, which innervate the TIDA neurons and inhibit their activity during the dark phase to entrain the timing of the reduction in dopamine and the nocturnal surge of prolactin (Poletini et al. 2010). Noradrenergic inputs to the ventromedial hypothalamus also appear to be critical in transmitting this mating response (Northrop et al. 2006; Northrop and Erskine 2008), perhaps acting on the oxytocin receptor-containing neurons in this region, as pharmacological blockade of alpha1 adrenergic receptors in this region will block the induction of prolactin surges. Opioid-induced suppression of dopamine may also be required, as blockade of kappa or mu opioid receptors will also block the prolactin surges (Andrews and Grattan 2002, 2003). After initiation, reciprocal feedback between prolactin and dopamine is then thought to sustain the prolactin surges over multiple days until it is termination by chronic, placental lactogen-induced activation of the TIDA neurons.

1.4.4 Other Rapid Responses Associated with the Maternal Recognition of Pregnancy

A number of additional physiological changes occur rapidly in early pregnancy and may contribute to (or be dependent on) the maternal recognition of pregnancy. These may be induced independently by mating, or changed in response to the mating-induced changes in hormones.

1. Oxytocin release within the hypothalamic paraventricular nucleus is elevated during mating, and even more so if the oestrous female is able to control sexual interactions (i.e., under **paced mating** conditions) (Nyuyki et al. 2011). This might be part of the pathway whereby mating induces the prolactin surges (Northrop and Erskine 2008), as it is also known that these surges are optimally induced under paced mating conditions (Erskine 1995).
2. Within 14 h of mating in mice, core body temperature in females rises, arguably one of the earliest detectable signals that pregnancy is underway (Smarr et al. 2016) (see Fig. 1.2). This elevation results in daytime temperatures being significantly higher, manifesting as a flattening of the normal circadian variation between the dark (active) and light (inactive) periods. It seems likely that this reflects the thermogenic actions of progesterone, which will be rising in response to the rescue of the corpus luteum. Changes in core body temperature can be used to stage the different phases of the menstrual cycle, with significantly elevated temperatures observed in the luteal phase.
3. There is also a reduction in locomotor activity seen very early in pregnancy, although this effect is reportedly much less consistent than the change in core

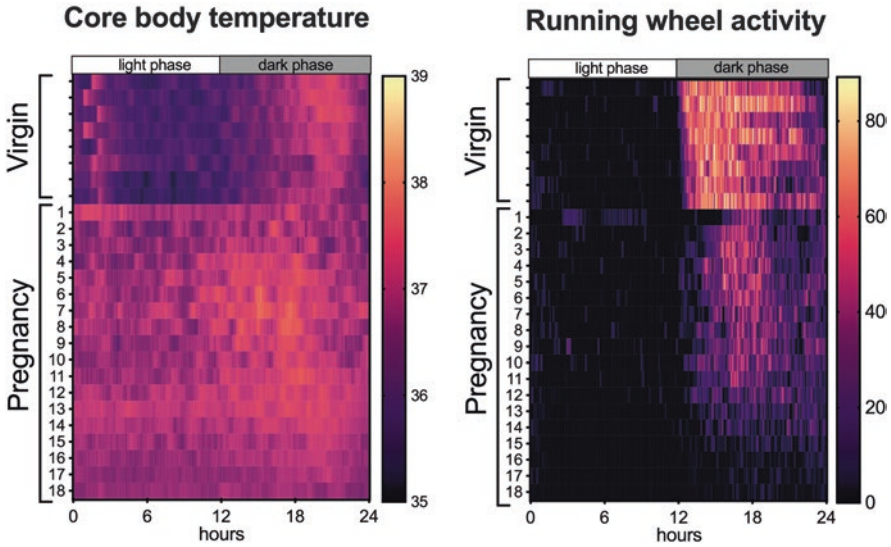

Fig. 1.2 Body temperature and activity in early pregnancy. Heat maps showing rapid changes in core body temperature (left) and running wheel activity (right) in the mouse in early pregnancy, starting immediately after mating (our unpublished data, based on the observations from Kreigsfeld's group (Smarr et al. 2016)). Data are generated from conscious, freely behaving animals using remote recording from implanted telemetry devices. The data are pooled from ten animals (core temperature) and eight animals (running wheel) recorded continuously before and during pregnancy. The heat maps show the normal circadian variation in core body temperature and running wheel activity seen before pregnancy, with temperature and activity lower in the light phase (when mice sleep), and higher in the dark phase (when mice are awake). These variables are rapidly altered on day 1 of pregnancy in the mouse (pregnancy day is given on the y axis). *Left panel*: Core body temperature (colour scale, as indicated on right of each figure, represents °C) immediately rises, and higher temperatures are then sustained, particularly in the light phase, such that the circadian pattern is largely lost. Temperatures remain high in pregnancy, until falling slightly in the last few days of pregnancy. *Right panel*: Physical activity (colour scale represents metres travelled on the running wheel per 5 min) is also rapidly reduced on day 1 of pregnancy, and this reduced activity is maintained throughout the pregnancy. These changes occur prior to implantation, and so must be driven by hormonal changes associated with mating (evidence of the maternal recognition of pregnancy)

body temperature (Smarr et al. 2016). Voluntary running wheel activity is also dramatically reduced very early in pregnancy (Fig. 1.2), an effect that seems to be driven by elevated prolactin, acting in the preoptic region of the brain (Ladyman et al. 2021).

All of these changes occur very early in pregnancy, prior to the implantation of the embryo, and are therefore driven by the hormonal changes associate with mating. Thus, mating-related signals provide a surrogate indicator for the maternal recognition that pregnancy is possible.

1.5 Conclusion

Maternal recognition of pregnancy is necessary to initiate the appropriate adaptations to maintain progesterone secretion. In humans and other animals with a long luteal phase, this typically involves the early production of a chorionic gonadotropin from the implanted conceptus to signal to the ovary and maintain corpus luteum function. In animals such as rodents, with a spontaneous luteal phase that is too short to last until implantation and initial formation of the placenta, the mating stimulus provides a surrogate for the maternal recognition of pregnancy and initiates a number of hormonal changes. The most prominent of these is the mating-induced release of prolactin, which serves the same purpose as chorionic gonadotropin, rescuing the corpus luteum and maintaining progesterone secretion. This initial recognition of pregnancy is followed by further elaboration of placental endocrine functions, and the characteristic of the feto-placental takeover of the maternal endocrine system (in whole or in part) to enable patterns of hormone secretion that facilitate foetal development. These placental hormones contribute to the wide range of pregnancy adaptations described in other chapters of this book.

Perspectives

The "maternal recognition of pregnancy" is a critical process, and in the context of topics covered in this book, it initiates the neuroendocrine adaptations in the mother during pregnancy. However, there is large species variation in the mechanism of maternal recognition of pregnancy, making investigation complicated. Critical health problems, such as miscarriage, need better understanding, but it is important to determine suitable biomedical models for investigation. Future research must focus on what mechanisms are unique to the model in question, and that are common across mammals and therefore might directly inform translational outcomes. For research into the neuroendocrine adaptations to pregnancy, the specific mechanism underlying initial maternal recognition of pregnancy in the different experimental models might not be important, because the consequent hormone-induced changes in function might be similar. It is important that researchers understand these processes, however, so that appropriate conclusions and translational inferences can be made.

Key References (See the Reference List for Citation Details)

Bazer (2015). Provides an overview of the origins of the concept of "maternal recognition of pregnancy", and a thorough description of the range of species differences in this process.

Bertram et al. (2006). Provides the theoretical understanding of how a pattern of twice-daily prolactin surges can be generated from a single stimulus (mating). This formed the basis of much experimental work to elucidate the pathways involved.