

## REPRODUCTIVE PHARMACOLOGY

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## Summary

This chapter presents an outline of reproductive pharmacology, an important subject with applications in all aspects of reproductive and sexual health.

Glands of importance in sexual development and reproduction include the gonads, the pituitary gland, and, in pregnancy, the feto-placental unit. Their function is regulated by hypothalamic, anterior pituitary or placental peptides. A number of pharmacological agents are used to modify or manipulate the release and actions of the hormones produced by these glands, and in replacement treatments for hormonal deficiencies. Section 2 focuses on these glands, the hormones they produce and the receptors at which these hormones act. Also discussed are the receptors for prostanoids of known importance in reproductive function.

Section 3 comprises a brief overview of the hormonal control of testicular function.

The menstrual cycle is a cycle of interdependent ovarian, uterine and hormonal changes, and a time of transient fertility. There are numerous menstrual cycle disorders which lead to significant health and economic costs. Treatment of these disorders depends heavily on the use of endocrine drugs. Pharmacological interventions can also be used for the control of fertility, with contraception, or for management of some infertile couples. Sections 4 and 5 focus on the menstrual cycle, its disorders and treatment, and drugs affecting fertility and conception. The use of hormonal agents in management of some symptoms associated with the menopause is also addressed.

Section 6 is concerned with the use of drugs in pregnancy, parturition and lactation.

A variety of environmental agents pose a potential threat to the reproductive health of women and the health of the developing fetus. In pregnancy, both the mother and the unborn baby are at risk, due to increased sensitivity of both to these agents. Section 7 deals with endocrine disrupting chemicals, their actions and our likelihood of exposure to them, and gives examples of three such chemicals and Section 8 finally concludes this chapter with a few remarks.

## **1. Introduction**

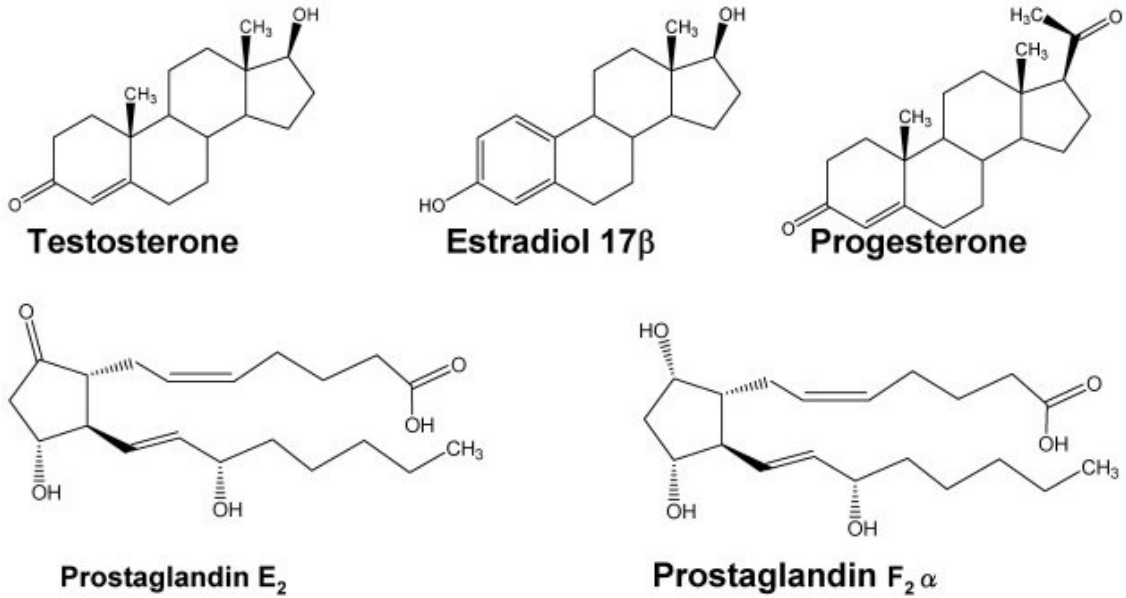
Reproductive pharmacology is an area which has flourished since approximately the middle of the twentieth century. Reliable pharmacological control of human fertility has resulted in far-reaching changes in the lives of individuals and communities where it is available. Many of the improvements in maternal and infant morbidity and mortality are due to pharmacological interventions where they are within the reach of the people. Increasing specificity of treatments for the various disorders and discomforts of reproductive system function has increased the quality of life of many women, and reduced health and economic costs. Treatment of infertility shows increasing success: this is a growing industry which often now relies on specific pharmacological intervention. Reproductive pharmacology is a vast topic with applications in all aspects of reproductive and sexual health.

## **2. Reproductive Glands and Hormones and Their Regulation**

A number of the hormones of importance in reproduction and development are shown in Figure 1 and Table 1.

Endocrine glands of importance in sexual development and reproduction in males and females include the gonads and the pituitary gland. Their function is regulated by peptides including gonadotrophin releasing hormone (GnRH) formed in the hypothalamus. The effects produced by the hormones they release depend on several factors including the nature of the target tissues and the receptors present in those tissues. For example, in the uterus the sex steroid estrogens affect the growth of the endometrium while in hypothalamus they affect the release of GnRH. The receptors for hormones may be located on cell membranes or in the cytoplasm or nucleus. In the former case the actions usually occur more rapidly compared to the latter in which the

activation of the nuclear receptor leads to the formation of proteins. Different cells may produce the same hormones, for example the fetoplacental unit in pregnancy can, like the ovary, produce estrogens and progesterone as well as a gonadotrophin, human chorionic gonadotrophin (hCG) which can exert similar actions to those of luteinizing hormone (LH).



**Oxytocin:** Cys-Tyr-Phe-Glu-Asp-Cys-Pro-Arg-Gly  
**GnRH\*:** pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly CONH<sub>2</sub>  
 \*Gonadotrophin Releasing Hormone

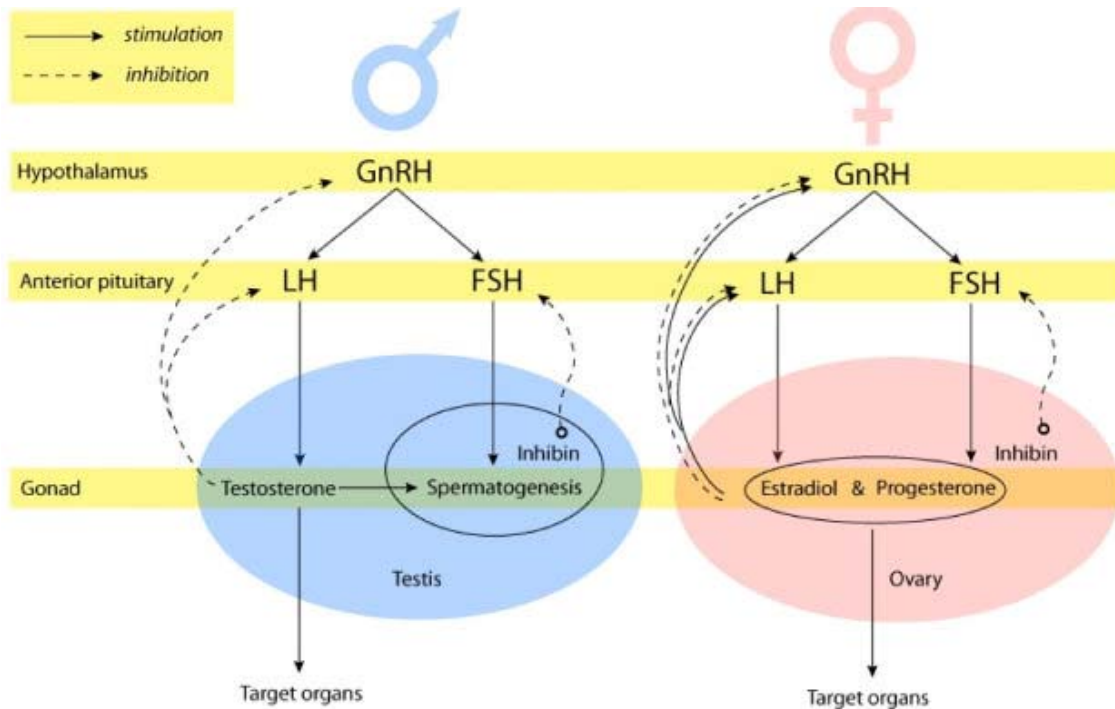
Figure 1. Formulae and sequences of some hormones of importance in reproductive function

<i>Hormone</i>	<i>Main Origin</i>	<i>Role</i>
Testosterone	Leydig cells in testes	Development of male reproductive tract and sexual behavior, spermatogenesis, stimulation of bone and muscle mass
Dihydro-testosterone	Formed in androgen target tissues by action of 5-alpha-reductase on testosterone	Masculinization of external genitalia, body and facial hair development, maintenance of accessory reproductive tract tissues, e.g. prostate
Estradiol 17β	Developing follicle and corpus luteum of ovary	Development of female reproductive tract and secondary sex characteristics. Feedback regulation of release of GnRH from hypothalamic neurones, oogenesis,

		endometrial proliferation, development of mammary tissue in pregnancy
Estriol	The fetoplacental unit in pregnancy	Essential in pregnancy maintenance
Progesterone	Ovarian corpus luteum, and placenta	Promotes secretory endometrium and essential in pregnancy maintenance
Follicle stimulating hormone (FSH)	Gonadotroph (basophil) cells of anterior pituitary gland	Stimulates ripening of ovarian follicles in the female and stimulates spermatogenesis in the male
Luteinising hormone (LH)	Gonadotroph (basophil) cells of anterior pituitary gland	Causes ovarian follicle rupture in female and maintains corpus luteum; production of testosterone in Leydig cells
Chorionic gonadotrophin	Placental villi	Takes over function of LH during early pregnancy to maintain corpus luteum
Prolactin	Lactotroph (acidophil) cells of anterior pituitary gland	Development of mammary glands and lactation
Oxytocin	Posterior pituitary gland	Important in labor and in milk ejection in lactation
Gonadotrophin releasing hormone (GnRH)	Hypothalamic neurones	Stimulates FSH and LH release from gonadotrophs
Inhibin	Ovary, testes	Inhibits release of FSH

Table 1. Hormones of importance in reproduction and development.

Figure 2 illustrates the hypothalamic-pituitary-gonadal axis, the hierarchy controlling sexual development and reproduction. It shows the sites of hormone formation and release together with the feedback loops in the human. The gonads comprise the ovaries in the female and the testes in the male. These glands produce the germ cells, i.e. the eggs (*ova*) in the female (see Sections 2.3 and 4.1.1), and the sperm (*spermatozoa*) in the male (see Section 3.0). They also produce the female and male sex hormones which are formed and released in response to hormones formed in and released from cells in the anterior pituitary gland. In turn the hormones produced in the gonads can feed back and modify the formation and release of the hormones from the anterior pituitary gland either directly or indirectly by acting on the hypothalamic region of the brain, which contains neurosecretory cells that release GnRH that acts on the pituitary gland. The pituitary hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH), act directly on the gonads and others, for example oxytocin and prolactin act directly on reproductive organs including the uterus and mammary glands respectively.



The hypothalamic-anterior pituitary-gonadal axis describes the hierarchical control of gonadal function in the human male and female. Gonadotrophin releasing hormone (GnRH) from the hypothalamus stimulates anterior pituitary gland secretion of luteinising hormone (LH) and follicle stimulating hormone (FSH). Gonadal function, including sex hormone secretion, is controlled by LH, FSH and inhibin, which is of gonadal origin. Hormone secretion is either stimulated or inhibited.

Figure 2. Diagram showing some sites of hormone formation and release together with the feedback loops in the human

### 2.1. The Hypothalamic Factor

GnRH is a decapeptide (see Figure 1) synthesized in the hypothalamus and transferred via the hypothalamic–hypophyseal portal system to the anterior pituitary to regulate the release of the gonadotrophins. It is formed in neurones in the arcuate and other nuclei of the median eminence. It is secreted in a pulsatile manner and regulates the release of the reproductive hormones FSH and LH from the anterior pituitary. The release of GnRH is in turn affected by circulating levels of gonadal hormones and by the central nervous system.

In mammals GnRH acts at two receptors designated Type 1 GnRHR and Type 2 GnRHR. The Type 1 receptors are expressed in pituitary gonadotrophs and regulate gonadal function. They differ from many other seven transmembrane receptors in lacking C-terminal tails. A range of synthetic agonists, including buserelin, as well as antagonists, have been developed and are used therapeutically in the management of infertility (see Section 5.3). Loss-of-function mutations in Type 1 receptors are associated with hypogonadism.

## 2.2. The Pituitary Hormones

The pituitary gland, situated at the base of the skull consists of two main parts, the adenohypophysis or anterior pituitary gland and the neurohypophysis or posterior pituitary gland. These regions secrete several hormones, some of which play a primary role in the regulation of gonadal function. Only the latter are discussed herein. These are the peptides FSH and LH. In the female, FSH acts on the ovary to stimulate follicle growth and hence ovum development, and LH promotes the development of the *corpus luteum*. Both act in concert to stimulate the release of sex steroids. In the male, FSH acts on the testes to stimulate the growth of sperm while LH stimulates the release of testosterone.

FSH and LH are glycoproteins with different subunits. These and the related hormone hCG, produced by the human placenta during pregnancy, are heterodimers with alpha and beta subunits, the latter dictating their selectivity. In women, release of each gonadotrophin is independently regulated. FSH and LH stimulate release; estrogens and inhibin negatively regulate FSH and LH release through an action at the hypothalamic level (Figure 2). In males the release of the two hormones is synchronous, with LH pulses greater than FSH. In females their pattern of release varies during the menstrual cycle, with preovulatory surges of both hormones occurring (see Section 4.1.3). In the menopause the levels, particularly of FSH, increase because of the lack of inhibition by ovarian hormones. Impairments in pituitary function can lead to developmental problems in both men and women.

Pituitary and placental gonadotrophins act at specific G protein-coupled receptors on target cell surfaces. The cDNAs corresponding to the LH receptor (LHR) and to the FSH receptor (FSHR) have been cloned. Like other G-protein coupled receptors, the N-terminal extracellular portion binds the hormones, whereas the C-terminal membrane-associated portion is responsible for receptor activation. LH and FSH receptors can form functional homo- and hetero-dimers. Naturally occurring mutations in the LH/hCG receptor (R) and the FSHR have been demonstrated to produce alterations in development. One such example is in familial male precocious puberty when the LHR becomes constitutively active. The roles of the gonadotrophins and their receptors in testicular function, and the menstrual cycle and pregnancy are described in Sections 4, 5 and 6.

A third anterior pituitary hormone, prolactin, promotes mammary gland development and lactation in the female. Its role in the male remains uncertain. It is a single chain polypeptide of 199 amino acids with three disulphide bonds, formed in the lactotrophs of the anterior pituitary. Levels increase in pregnancy and in suckling mothers. It is secreted in a pulsatile fashion. The hypothalamic control is predominantly inhibitory and is mediated by dopamine. Unlike other pituitary hormones it is not subject to feedback regulation by substances in peripheral target cells, although its secretion is affected by estrogens. Its target cells include the mammary glands, where it initiates lactation in the post-partum period; it also suppresses the menstrual cycle. In non-pregnant women it plays no role in the control of ovarian function.

The posterior pituitary gland is neural in origin and produces two hormones, antidiuretic hormone (vasopressin) and oxytocin. Only the latter has an established role in reproductive function playing a role in parturition (birth) and in the ejection of milk from the mammary glands. It is a decapeptide (Figure 1) with one cysteine bridge which has some similarity with arginine vasopressin (or antidiuretic hormone). Its levels peak during parturition and lactation, and increase in response to vaginal and nipple stimulation. Oxytocin is also synthesized in uterine tissues.

Oxytocin designated OT acts at 7 transmembrane-spanning G-protein coupled receptors (7 TM receptors). It also has some action at vasopressin V<sub>1a</sub>, V<sub>1b</sub> and V<sub>2</sub> receptors; V<sub>1a</sub> receptors are present in the uterus. Vasopressin, which has been implicated as playing a role in dysmenorrhea (see Section 4.0), also has action at OT receptors. Myometrial OT receptors increase under estrogen dominance and there is also an increase in their numbers during parturition. As well as mediating uterine contraction directly, oxytocin can also enhance release of prostaglandins (see Section 6.1) so indirectly facilitating parturition. In the non-pregnant human uterus, oxytocin, in contrast to vasopressin has little effect. The uses of oxytocin in obstetrics are described in Section 6. No synthetic analogues have been developed for use in obstetrics. However it has been proposed that the V<sub>1a</sub> and OT receptor antagonist, atosiban, is of potential application for use as a tocolytic agent in preterm labor. Oxytocin is thought to play no important role in reproductive function in males or in non-pregnant women.

### 2.3. The Gonadal Hormones

The best understood gonadal hormones are the sex steroids, estradiol, testosterone and progesterone (Figure 1). A number of related steroids which mimic or mediate their actions are also produced in the body, while a number of synthetic steroids that mimic or modify their actions are used as pharmaceutical agents. Steroids are formed from cholesterol and thus are fat soluble and travel in the blood stream bound to plasma proteins. They must be released from these proteins to exert their biological actions. Therefore levels of these binding proteins can affect their availability for action. Ultimately the gonadal steroids in both men and women are broken down in the liver to less active and often more water soluble compounds which are either recycled or excreted from the body.

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### Biographical Sketches

**Jo Pennefather** is a pharmacologist, graduating with a PhD in Pharmacology from the University of Sydney in 1961. Following post doctoral appointments in London UK, Minneapolis USA and Melbourne Australia, she was appointed to a continuing academic position in the Department of Pharmacology at Monash University in 1976. Since 2000 she has held honorary appointments as Associate Professor in the Department of Obstetrics and Gynaecology, Royal Women's Hospital, University of Melbourne, and currently in the Department of Pharmaceutical Biology Victorian College of Pharmacy, Monash University.

Her interests and her publications (over 100) include research into hormonal and neural influences on the genito-urinary tract.

Dr Pennefather is a consultant to the Editorial Board of the *European Journal of Pharmacology* and a life member of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, and a retired member of the British Pharmacological and the Australian Physiological Societies. She is also a member of the Australian Federation of University Women and WISENET.

**Claire Garrett** BSc (Hons) University of Melbourne, PhD Australian National University

She has a background in physics and is currently a research fellow in the Department of Obstetrics and Gynaecology at The University of Melbourne. Her field of research is male infertility, and in particular the application of image analysis to objective assessment of human sperm morphology and prognosis of fertility.

Dr Garrett has also applied mathematical modeling techniques to a variety of biological problems, helping to quantify some interesting areas of research involving human sperm-oocyte interactions in vitro, hormone induced suppression of spermatogenesis and cervical mucus penetration by sperm.

For this publication Claire has enjoyed taking on the role of illustrator.

**Luba Tomaska** is a regulatory scientist, graduating with a PhD in Immunology at the John Curtin School of Medical Research, Australian National University. She has more than a 20-year experience in regulatory toxicology, regulatory policy and risk analysis, dealing with the human risk assessment and risk management of chemical and microbiological agents, within the Australian Department of Health. In the last 10 years she has contributed to a number of the World Health Organization and other publications dealing with the methodology and assessment of risk to humans posed by chemicals.

**Elizabeth Brown** graduated from the University of Melbourne with an MSc in reproductive biology, and a Dip Ed. She has a particular interest in the biological basis of reproductive and sexual health, and in education as a means for the promotion of health and well-being. She has extensive experience as a teacher, especially to students in the health sciences at La Trobe University, in Melbourne, Australia. A central part of her teaching focuses on applications of pharmacology and physiology for the promotion of reproductive and sexual health. She has had continuing academic appointments since 1975. In addition to teaching, Elizabeth also has a research interest in human fertility and the factors that affect it.

Elizabeth Brown is a member of a number of societies, including the Fertility Society of Australia, and the Australian Physiological Society.

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