SEXUAL AND REPRODUCTIVE HEALTH

A PUBLIC HEALTH PERSPECTIVE

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AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD
PARIS • SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
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ACADEMIC PRESS

Academic Press is an imprint of Elsevier
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
32 Jamestown Road, London NW1 7BY, UK
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The Chapter on *Worldwide Burden of Gynecologic Cancer: The Size of the Problem* by Sankaranarayanan and Ferlay was previously published under the title of *Worldwide burden of gynaecologic cancer: The size of the problem* in Best Practice & Research Clinical Obstetrics and Gynaecology 20[2]: 207–225, 2006. The chapter on *Cervical Cancer* by Zeferino and Derchain also previously appeared in the same journal (20[3]: 339–354, 2006) under the title *Cervical cancer in the developing world*, and the chapter on *Endometrial Cancer* by Sonoda and Barakat was also previously published by this journal (20[2]: 363–377, 2006) under the title *Screening and the prevention of gynecologic cancer: Endometrial cancer.* Minor updating and adaptation were made in all three articles for the purposes of the present book.

All other material originally appeared in *The International Encyclopedia of Public Health*, edited by Kris Heggenhougen and Stella Quah (Elsevier Inc., 2008)

Library of Congress Cataloging-in-Publication Data

Sexual and reproductive health: a public health perspective/editor-in-chief, Paul van Look; editors, H.K. Heggenhougen, Centre for International Health, University of Bergen, Norway, Department of International Health, Boston University School of Public Health, and Department of Global Health and Social Medicine, Harvard Medical School, Stella R. Quah, Duke-NUS Graduate Medical School Singapore, Singapore.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-12-385009-6 (hardback : alkaline paper)
1. Reproductive health services. I. Look, Paul F. A. van, editor. II. Heggenhougen, Kris (Kristian), editor. III. Quah, Stella R., editor.
[DNLM: 1. Reproductive Health Services. 2. Family Planning Services. 3. Perinatal Care. 4. Pregnancy Complications–prevention & control. 5. Reproductive Rights. 6. Sexually Transmitted Diseases–prevention & control. WQ 200]
RA652.S49 2011
613.9–dc22

2010046204

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-385009-6

For information on all Academic Press publications
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PRINTED AND BOUND IN USA
10 11 12 13 10 9 8 7 6 5 4 3 2 1

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PREFACE

This volume presents the highlights of current global thinking about sexual and reproductive health. Major changes have taken place in the last 15 years in the way decision-makers think about the subject and the manner in which programs deliver comprehensive sexual and reproductive health services. The turning point was the International Conference on Population and Development (ICPD) held in Cairo, Egypt, in 1994. ICPD was a watershed for several reasons. First, more than in any of the preceding United Nations population conferences, the issue of population was clearly placed as being central to sustainable development. Second, the narrow focus on population growth ('the population bomb'), which had been a neo-Malthusian concern and preoccupation ever since the Club of Rome published its 1972 report *Limits to Growth*, was replaced by the comprehensive concept of (sexual and) reproductive health. Third, and linked to the definition and introduction of the reproductive health concept, was the strong call for a paradigm shift away from a policy environment driven by demographic considerations (sometimes to the point of using coercion in family planning services in order to reach demographic targets) to an environment that recognized the right of individuals to make their own choices. Last but not least, ICPD as well as the Fourth World Conference on Women (FWCW) held the following year in Beijing, People's Republic of China, strongly emphasized that the rights of women and men to good sexual and reproductive health are firmly grounded in universal human rights.

At the same time, however, the debates that took place both at ICPD and at FWCW, and in many other fora since then, amply demonstrate the difficulties some people had, and continue to have, with internalizing the concept of sexual and reproductive health in all of its dimensions, given that it embodies some of the most intimate and personal aspects of our lives as human beings. Even in some of the most broad-minded and liberal societies, subjects such as sexual education for and the sexuality of young people, induced abortion, sexual violence against women, sexual orientation, and sexual dysfunction, to name but a few, continue to be avoided in public discourse and can be considered taboo subjects for discussion altogether. This may, to some extent, explain why we seem to have such difficulty in making headway with tackling some of the obstacles that still encumber the achievement of good sexual and reproductive health by all.

When looked at from a global perspective, as this book tries to do, there is another striking characteristic in the field of sexual and reproductive health, namely the immense gap that exists between the developed and developing countries, between the rich and the poor. Perhaps in no other branch of health is this inequity so great. Take, for instance, the risk of dying a woman has when she becomes pregnant. Globally, according to the latest figures from WHO, UNICEF, UNFPA, and The World Bank, some 358,000 women died in 2008 from causes related to pregnancy, delivery, and the immediate period after delivery; more than 99 per cent of these deaths occurred in developing countries. A sub-Saharan woman who becomes pregnant is nearly 100 times more likely to die from a pregnancy-related cause than a woman in a Western European country; for some developing countries such as Afghanistan, Chad, Guinea-Bissau, and Somalia, the risk is 140 times or more. Similarly, unmet needs for good-quality contraceptive methods and services remain huge in many areas of the world, particularly in sub-Saharan Africa, and sexual transmission of the human immunodeficiency virus (HIV), the cause of the acquired immune deficiency syndrome (AIDS), is also strongly concentrated in developing countries, again particularly in sub-Saharan Africa, where in several countries AIDS is having a major impact of shortening life expectancies.

Some 15 years have gone by since the global community met at ICPD and FWCW. Nevertheless, sexual and reproductive health and rights continue to catch the limelight, perhaps even more so in the last few years now that the overriding goal of ICPD ('achieve, by 2015, universal access to reproductive health') has finally been formally integrated into the Millennium Development Goals (MDGs) framework as one of the two targets under MDG 5 ('improving maternal health'). Thus, the present time seems most auspicious for this volume with its specific focus on sexual and reproductive health and rights looked at through a global public health lens.

This book, which we hope will become a valuable tool in your daily work, attempts to capture the comprehensive, and often complex and politicized, field of sexual and reproductive health and rights. It comprises 37 chapters; 34 of these are

taken from the *International Encyclopedia of Public Health* published by Elsevier in 2008 and the remaining three (on the worldwide burden of gynecologic cancer, on cervical cancer, and on endometrial cancer) are slightly adapted and updated versions of papers published elsewhere. Given that all chapters address aspects within the theme of sexual and reproductive health, there is some inevitable overlap between some of the chapters and some authors go beyond the theme of sexual and reproductive health. For instance, the chapter on cancer screening also has some general information on the predictive value of screening tests and the organization of screening programs as well as information on screening for lung and colorectal cancers in addition to screening for cervical, breast, and prostate cancers. We believe, however, that this additional material, rather than being distractive, helps to put the information on sexual and reproductive health issues in a wider context.

The 37 chapters are divided into four sections. The first section has nine chapters dealing with human reproductive physiology (female and male reproductive function, puberty, and menopause) and the basic underpinnings of sexual and reproductive health. It also contains chapters on demography (population growth and trends in fertility) and perinatal epidemiology; the latter topic has been included since perinatal outcomes, in particular stillbirths and early neonatal deaths, are so much influenced by events happening during pregnancy and at the time of childbirth.

The second section focuses on the core elements that make up sexual and reproductive health as we understand it today. This section has, of course, chapters on the cornerstones of sexual and reproductive health, such as family planning, sexually transmitted infections, abortion, maternal mortality and morbidity, and infertility. But in this section you will also find chapters on sexual and reproductive health aspects that traditionally are not generally dealt with in a book of this nature. These aspects are, for instance, sexual violence and violence against women (often still considered taboo subjects), HIV/AIDS (which is, after all, very much a sexual issue in many parts of the world and linked closely to infant's health where there exists a risk of mother-to-child transmission of the virus), and the causes and outcomes of fetal growth retardation (which is often linked to the mother's condition during pregnancy).

The third section has eight chapters on the most common genital cancers in women (i.e., those affecting the uterine cervix, endometrium, breast, and ovary) and in men (cancers of prostate and testis). Of particular interest to readers may be the two chapters at the beginning of this section, namely those on cancer screening and on the global burden of gynecologic cancers, which is another telling example of the "North–South" divide although, in this instance, the picture is a mixed one with incidence rates for some cancers, notably cancer of the uterine body and ovarian cancer, greater in developed countries than in developing countries while the reverse is true for cancer of the uterine cervix.

The one single characteristic in sexual and reproductive health matters that has undoubtedly created the greatest public debate in recent times, ever since the birth of Louise Brown in 1978 following the successful *in vitro* fertilization of a human egg by a human spermatozoon, has been the ethical dimensions of applying various reproductive technologies in humans. Prime examples of these ethical debates in the recent past have been on the subject of the potential (mis)use of reproductive cloning (for instance to create a carbon-copy individual to serve as organ donor as evoked in the recent film *My sister's keeper* after the similarly named novel by Jodi Picoult) and on the harvesting of stem cells from human embryos for research with potential future clinical application in a range of degenerative and other ill-health conditions. It should not come as a surprise, therefore, that three of the eight chapters in the fourth and final section of this book are devoted to reproductive ethics. The other chapters in this section concentrate on some of the factors that can have a profound impact on sexual and reproductive health, namely, gender, the enjoyment (or lack thereof) of reproductive rights, and the cultural context in which women and men try to achieve their sexual and reproductive health goals. The final chapter in this section addresses the emerging recognition of the magnitude of women's mental ill-health, much of which is related to women's experience of sexual and reproductive events during the life course.

In compiling a book on an issue of such breadth, complexity, and sensitivity – at personal, community, national, and global levels – it is inevitable that a certain element of eclecticism enters the choice of articles. We do, nevertheless, hope that you will find this collection of papers most helpful in your work as an academician, policy maker, student, or other concerned professional with a passion for and dedication to improving the sexual and reproductive health and rights of our fellow citizens, wherever they may live. We are, of course, most interested to hear your comments and suggestions for possible future editions of this book.

Finally, in closing, we thank the plethora of distinguished authors who enthusiastically accepted the invitation to include their work in this volume. We also say a big 'thank you' to the Elsevier Editorial Team, in particular Nancy Maragioglio and Carrie Bolger, who made sure that we stayed on the "straight and narrow" of publishing deadlines and who were as committed as we were to make this book a valuable resource.

The Editors

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Female Reproductive Function

H B Croxatto, Chilean Institute for Reproductive Medicine, Santiago, Chile

Introduction

The organs most involved in reproduction in the female are made up of the genital tract and ovaries located in the lower part of the abdomen, the hypothalamus, and pituitary gland located at the base of the brain and the breasts (**Figures 1** and **2**). The female reproductive system is formed during embryonic and fetal development, reaching incomplete development at the time of birth. Further growth and acquisition of full functional capacity is attained after puberty, which unfolds between 9 and 13 years of age. At puberty, the hypothalamic-pituitary-ovarian-uterine axis is activated and ovarian and endometrial cycles (**Figure 3**) become manifest by the occurrence of menstruation with a monthly periodicity. The first menstruation (or menarche) marks the onset of the fertile segment of a woman's life or reproductive years, in which women can conceive and give birth to one or more children. The number of oocytes (female gametes) present in the ovaries at birth is limited to a few hundred thousand or less and their number decreases thereafter continuously through a resorption process known as atresia. As a consequence, around the age of 50 years, the pool of oocytes becomes exhausted, ovarian and endometrial cycles cease to occur, and reproductive capacity wanes after the last menstruation (or menopause).

Menstruation and the Menstrual Cycle

The vast majority of vertebrates exhibit reproductive cyclicity as they can bear offspring repeatedly, but with a periodicity that is entrained with environmental phenomena determined by the Earth's rotation and yearly circling around the Sun. Other than parturition or egg-laying, an outstanding external signal of reproductive cyclicity is the female's behavior in response to male attempts to copulate. In most species, the female does not allow copulation except for a short period of hours or a few days preceding ovulation (the release of one or more oocytes from the ovary), enhancing in this way the probability of becoming pregnant. With the exception of the human and a few other species, mating is precisely timed to optimize the likelihood of fertilization (union of male and female gametes) and therefore reproduction.

This female receptive behavior toward mating is known as heat or estrus, hence the cycle in these animals is called the estrous cycle. This stereotyped receptive behavior toward mating is practically absent in the human female since women engage in sexual intercourse at any time of the menstrual cycle, during pregnancy, during lactational amenorrhea, and after the menopause. As a consequence, the vast majority of acts of sexual intercourse in the human are nonreproductive, affording only pleasant, uniting, and recreational experiences to the couple, without the invariable reproductive aim characteristic of most other animals.

The most prominent external sign of cyclicity during the reproductive years of the human female is menses or menstruation, which is blood mixed with tissue sloughed off from the superficial or functional layer of the endometrium (internal lining of the womb), being expelled through the vagina to the exterior. Thus, the cycle in women is called the menstrual cycle. Menses occur from menarche until menopause more or less regularly with a periodicity approaching the lunar cycle, and are temporarily suppressed during pregnancy and breastfeeding. While the occurrence of menstruation allows a woman to assume she is fertile, a delay in its occurrence, beyond its expected timing during the reproductive years in cycling, sexually active women, usually indicates that she has become pregnant.

At the time of impending menstruation or during menses, many women can experience a variety of unpleasant changes in mood and/or bodily sensations within a wide range of intensities, conditioned by the hormonal oscillations that cause menstruation. This, together with the sanitary requirements imposed by several days of vaginal bleeding, makes most women experience this monthly sign of cyclicity of their reproductive function with great awareness, although its importance and meaning varies considerably among them. Furthermore, different cultures assign a special meaning to menstruation and impose various rules on women that affect their social behavior or marital relationships while the bleeding episode is taking place. On the other hand, vaginal bleeding does not always reflect menstruation since there are diverse pathological conditions that are associated with blood loss from the endometrium or other segments of the female genital tract.

Menstruation is the culmination and external sign of the end of a nonconceptional cycle. It is immediately followed by the endometrial proliferative phase in which cells multiply to rebuild the functional layer that was sloughed off during menstruation (see **Figure 3**). The deeper or basal layer of the endometrium remaining after menstruation is no more than 3 mm in thickness

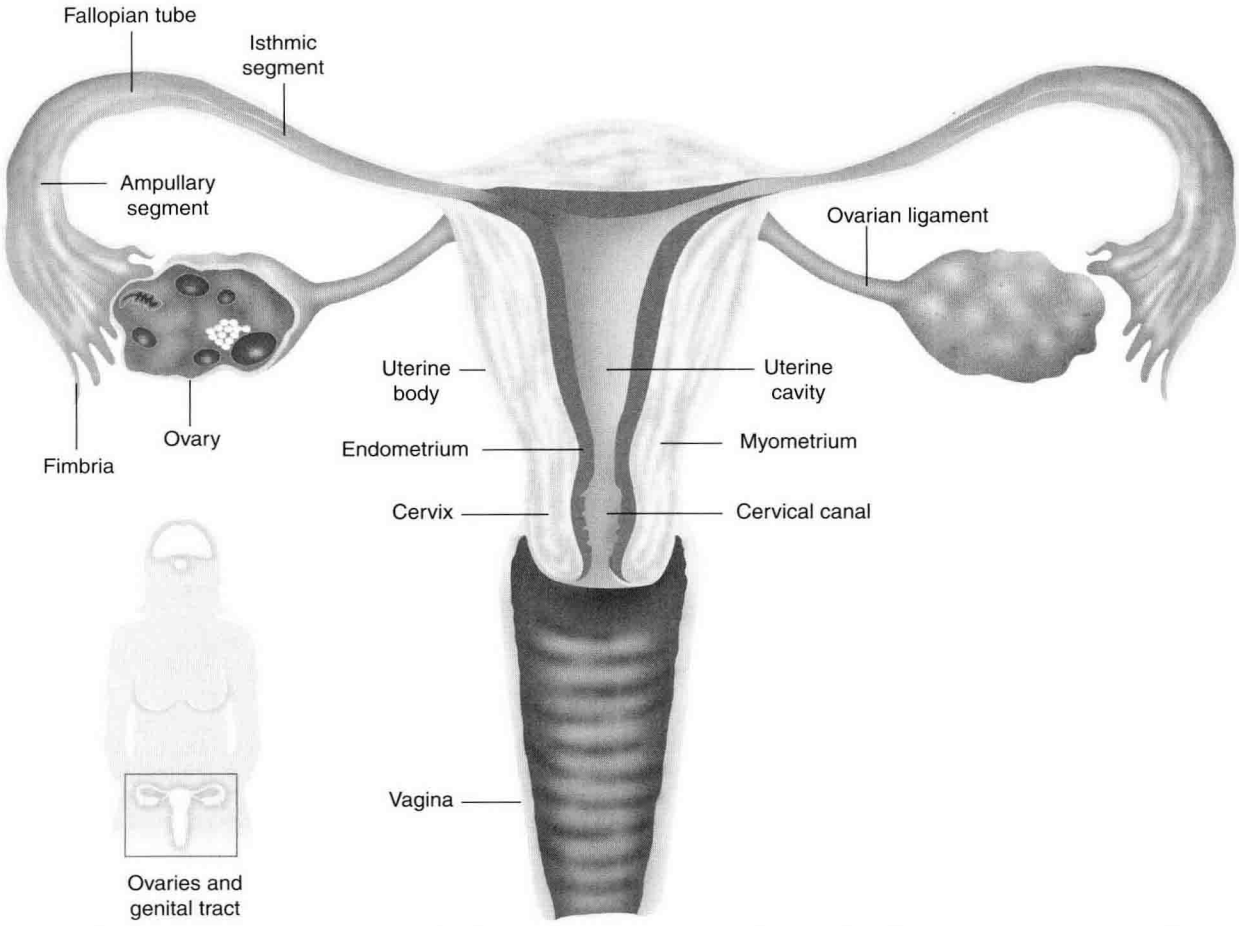

Figure 1 The female genital tract encompassing the ovaries, Fallopian tubes, uterus, and vagina. A partial frontal section allows appreciating the cavity of the tubular organs and the way they are connected.

and develops into a fully grown layer of up to 12–15 mm or more in about 2 weeks through stimulation by the increasing levels of estradiol (female hormone produced by the ovary) in blood. This proliferative phase is followed by a secretory phase in which tissue differentiation and remodeling and endometrial glandular secretion predominate under the influence of progesterone (another ovarian hormone) in preparation for nesting a fertilized egg (or zygote), if it should happen to be formed and arrive into the uterus in that cycle. The secretory phase also entails building the necessary mechanisms to produce menstruation if no zygote is formed during that cycle.

Recurrent sloughing off and rebuilding of the endometrium constitutes the endometrial cycle and takes place continuously for years until conception or the menopause occur. This process is not autonomous and is heavily dependent on estradiol and progesterone secreted by the ovary, therefore the endometrial cycle is precisely synchronized with the ovarian cycle (see **Figure 3**). Ovarian cycles are absent and ovarian hormone production is minimal or nil before puberty, during pregnancy and lactation, and after the menopause.

An outstanding feature of the menstrual cycle is its variability within and between women, not only in the intervals between menses but in their duration, in the timing of ovulation, the blood levels attained by the hormones involved, and several other parameters. The days of the cycle are usually counted taking the first day of menstruation as the first day of the cycle. Only for didactic purposes it is generally said that the menstrual cycle lasts 28 days and ovulation takes place on day 14 of the cycle. However, the normal cycle length varies from 21 to 35 days and follicular rupture can take place as early as day 10 or as late as day 22.

The Ovarian Cycle

The ovary plays a central role in female reproductive cyclicity and the menstrual cycle. Usually, the full ovarian cycle occurs in one of the two ovaries while the other exhibits incomplete waves of follicular growth for one or more cycles until the fully active side is reversed in a nonpredictable fashion.

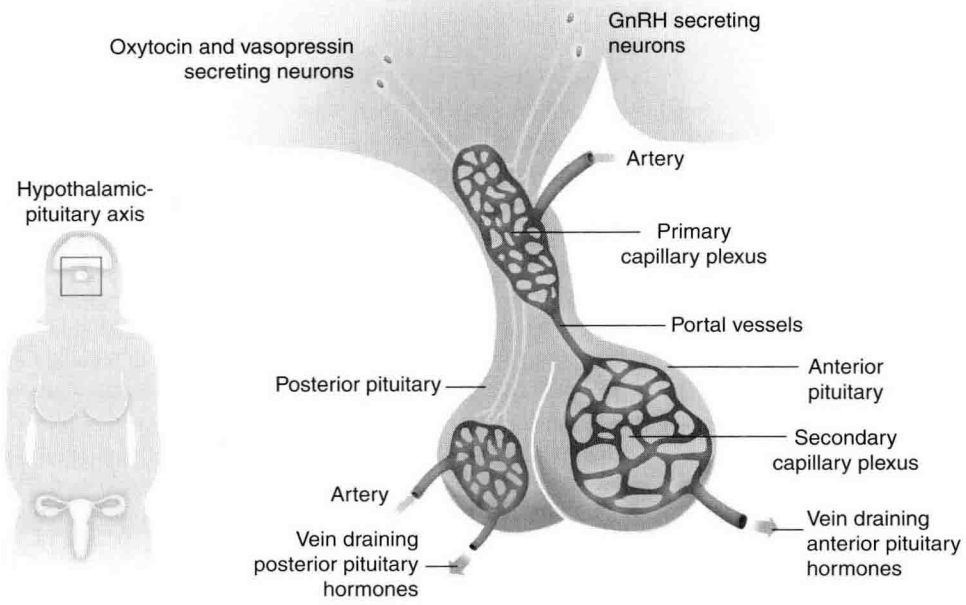

Figure 2 Components of the hypothalamic-pituitary axis most relevant to the reproductive process. Some neurons, which have their cell bodies located in hypothalamic nuclei, project their axons toward the primary capillary plexus of the hypothalamic-pituitary portal system where they deliver their hormonal secretions, notably gonadotropin-releasing hormone (GnRH). GnRH circulates down the portal vessels that resolve into the secondary capillary plexus in the anterior pituitary lobe. Here, GnRH diffuses out of the capillaries and acts on the gonadotrophs, stimulating the secretion of the gonadotropic hormones. Other hypothalamic neurons extend their axons all the way down into the posterior lobe of the pituitary where they release vasopressin and oxytocin, which are involved in parturition and milk ejection, respectively.

At the onset of each ovarian cycle, small antral follicles (tiny spheres containing each an oocyte and a fluid-filled cavity) grow rapidly stimulated by the gonadotropic hormones secreted by the anterior pituitary gland (**Figure 4**). Eventually, one of them becomes the leading or dominant follicle, which continues to grow to become a mature or Graafian follicle. A transient surge of the gonadotropic hormones in blood triggers the ovulatory process only in the mature follicle, leading to its rupture, release of the oocyte it contains and its transformation into a corpus luteum. The life span of the corpus luteum is self-limited to approximately 2 weeks, unless a developing zygote signals its presence. Functional demise of the corpus luteum allows both menstruation and the beginning of a new ovarian cycle.

The fundamental structures that sustain ovarian cyclicity come from a pool of thousands of primordial follicles, from which cohorts of about two dozen start growing every day in an autonomous manner. After a few months, nearly half a dozen reach the stage of antral follicle with a diameter of 2–5 mm while the rest undergo atresia at various stages of their development and disappear. The wall of antral follicles is formed by two layers of cells. The outermost layer is called the theca layer and is richly vascularized and innervated. The innermost layer, called granulosa, lacks vascular irrigation and innervation and is in direct contact with antral fluid. It is separated from the theca by a thin homogeneous lamina (basal membrane). Usually, each follicle contains a single oocyte that is immersed in the granulosa. The granulosa cells surrounding the oocyte form the cumulus oophorus during the ovulatory process.

Figure 5 shows a cross-section of a mature follicle which illustrates the layers forming its wall. From the outside to the inside: the external layer of cells forms the theca externa and interna. The theca externa is adjacent to the ovarian stroma (not shown). The theca interna is richly vascularized and innervated. A basal membrane separates the theca interna from the granulosa that lacks blood irrigation and innervation. The granulosa consists of several layers of cells housing a single oocyte and surrounding a cavity filled with follicular fluid. The cells immediately surrounding the oocyte (cumulus cells) behave differently from the rest of granulosa cells (mural granulosa). At ovulation, a mucinous material accumulates between them forming the cumulus

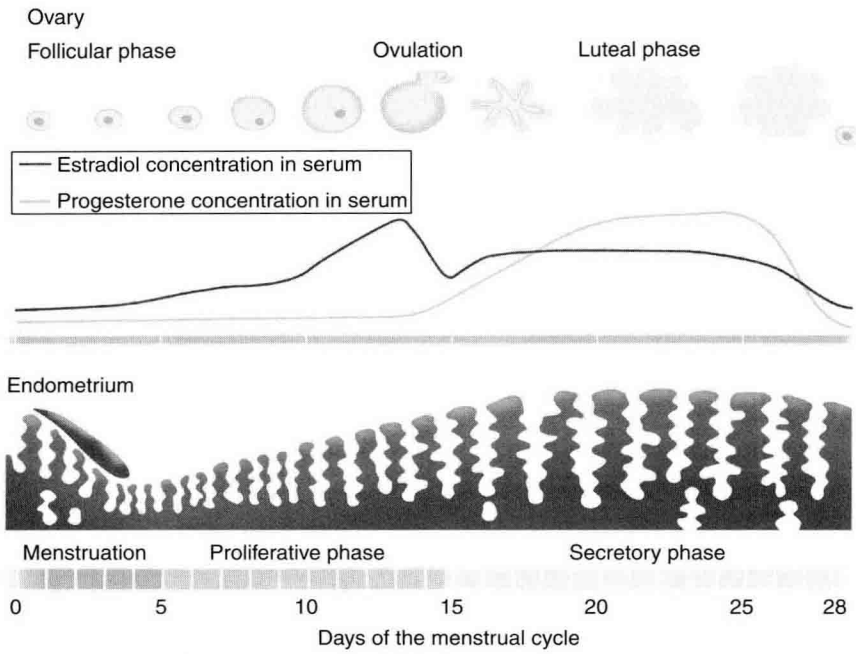

Figure 3 The upper part of this figure illustrates the phases of an ovarian cycle: the growth of a follicle in the ovary ending in ovulation and transformation into a corpus luteum that grows and then regresses and wanes. The middle part shows the oscillations in the blood serum concentration of estradiol and progesterone during the ovarian cycle. The lower part illustrates the phases of the endometrial cycle, beginning with menstruation. Increasing levels of estradiol secreted by the leading follicle as it grows stimulate cell proliferation and increasing thickness in the endometrium. The corpus luteum secretes both estradiol and progesterone in amounts proportional to its development. Progesterone stimulates glandular secretion and acquisition of receptivity to the blastocyst in the endometrium. Demise of the corpus luteum and associated decrease in estradiol and progesterone levels cause the onset of menstruation and of a new ovarian and endometrial cycle.

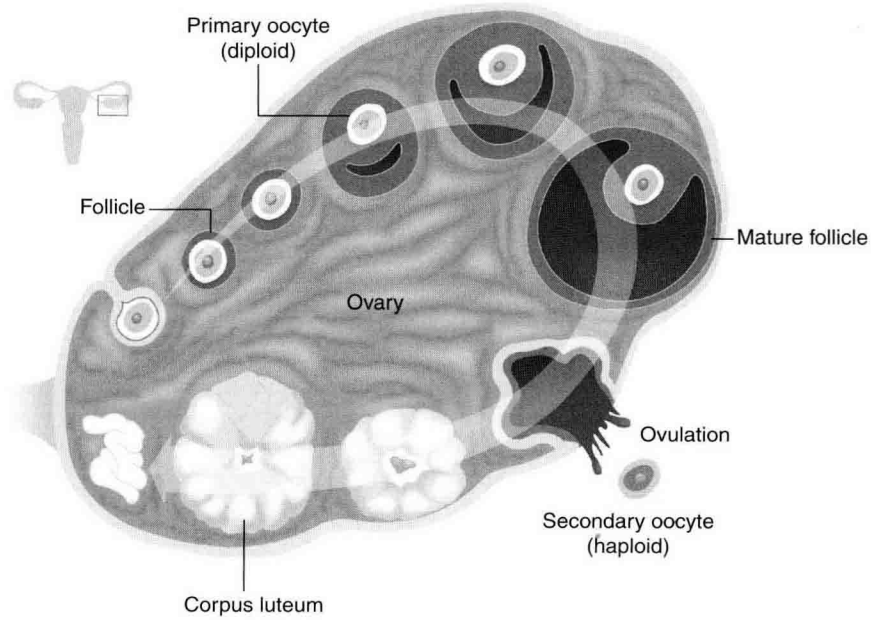

Figure 4 Life history of the follicle from a primary follicle destined to ovulate until ovulation, formation of a corpus luteum, and its demise in the ovary. See Figure 3 for the time frame of each stage.

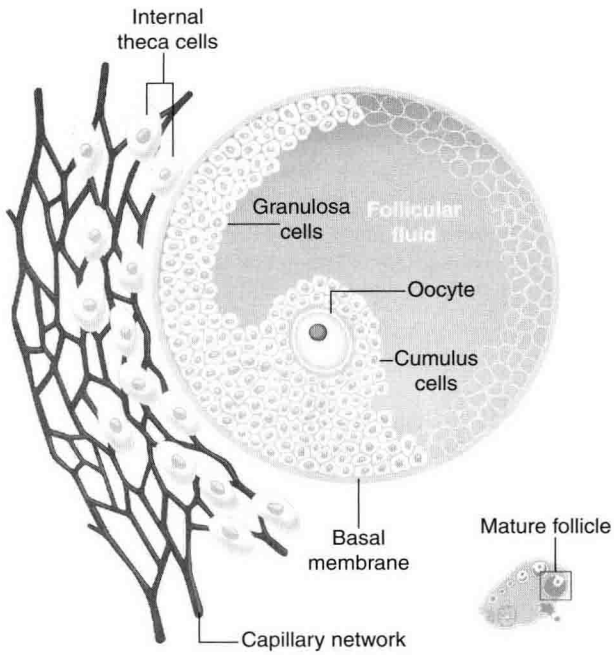

Figure 5 A cross-section of a mature follicle.

oophorus; they detach from the wall of the follicle and are released from the follicle surrounding the oocyte at ovulation. Theca cells respond primarily to luteinizing hormone (LH) by secreting androgens, whereas granulosa cells respond to follicle-stimulating hormone (FSH) and transform the androgens into estrogens.

At each transition from the end of one cycle to the beginning of the next, there is an elevation of FSH, a gonadotropic hormone in the circulation which acts to accelerate growth of the small antral follicles that began to develop months earlier. These follicles enter into a sort of competition until one of them becomes dominant and the others stop growing and undergo atresia. The dominant follicle continues growing by multiplication of its cells and accumulation of fluid in its cavity until reaching about 20 mm in diameter in 10–15 days. During this phase, the dominant follicle secretes increasing quantities of estradiol, resulting in an exponential rise in the blood level of this hormone until it surpasses a critical level that triggers a massive and transient release of the gonadotropic hormones, LH and FSH, from the pituitary gland. This surge of gonadotropic hormones acting on the mature follicle initiates the ovulatory process that will culminate 36 hours later in follicular rupture and release of the oocyte into a space that can be reached by spermatozoa to accomplish fertilization.

The ovulatory process is a complex series of parallel, synchronous, and, to some extent, independent changes affecting almost every component of the mature Graafian follicle. A crucial process is the resumption of oocyte meiosis that leads to extrusion of the first polar body (a small daughter cell resulting from oocyte division) containing one chromosome of each pair and, thus, the reduction of the number of maternal chromosomes within the oocyte to a single set. Another key process is the expansion of the intercellular matrix uniting the granulosa cells that surround the oocyte, to form the cumulus oophorus that detaches from the follicle wall so it can be extruded from the follicle at the time of follicular rupture and voiding. A third process is the activation of enzymes that erode the intercellular matrix of the follicle wall and allow the apex of the follicle to yield to the slightly positive pressure of the antral fluid, which is maintained throughout the entire process by the sustained contraction of the outer thecal cells at the base of the follicle. Both the granulosa and thecal cells begin a process called luteinization that entails major changes in steroid-synthesizing machinery leading to decreased synthesis of estradiol and increased synthesis of progesterone. The large amounts of progesterone to be produced in the following days impose increased energetic demands by these cells so granulosa cells secrete angiogenic factors that lead to disruption of the basal membrane and growth of newly formed blood capillary vessels into the luteinizing granulosa layer. Finally, the wall of the follicle ruptures at the apex, the follicle contracts, and the antral fluid containing the cumulus oophorus is voided toward the peritoneal cavity or directly to the fimbria of the Fallopian tube. Altogether these processes constitute ovulation.

Luteinized theca and granulosa cells remaining in the ruptured follicle reorganize to form the corpus luteum. They grow substantially in size, accumulate large amounts of lipids required for steroid hormone synthesis and, in the course of one week, they constitute the corpus luteum, a compact body in the superficial layer of the ovary that replaces the ruptured follicle (see **Figure 4**). During the second week after ovulation, the corpus luteum starts regressing and produces less and less progesterone and estradiol, which results in decreasing circulating levels of these hormones up to the point where the endometrium, lacking this hormonal support, starts to break down and menstruation ensues. The reduction in the circulating level of ovarian hormones weakens their negative feedback on gonadotropin secretion, allowing a transient small elevation of FSH that recruits a new cohort of antral follicles for initiating the next ovarian cycle.

The alternation of dominant follicle and corpus luteum as the predominant structure in the ovary gives rise to the denomination of follicular phase and luteal phase, respectively, to refer to these two phases of the ovarian cycle. These structural ovarian changes are accompanied by changes in the rate of secretion and blood levels of steroid and protein hormones produced by the ovary. The length of the follicular phase is more variable than that of the luteal phase and accounts for

most of the variability in the length of the menstrual cycle observed within and between women. The length of the luteal phase, taking as the first day the day in which the echographic image of the leading follicle shows it has collapsed, and as the last day the day preceding the onset of menstruation, varies from 9 to 16 days being 13 to 15 days in nearly 70% of the cycles.

The Endometrial Cycle

As the dominant follicle grows and secretes increasing amounts of estradiol, the cells located in the basal layer of the endometrium proliferate, endometrial glands and surface epithelium are reconstructed, and blood vessels grow again side by side with the endometrial glands. At the time of ovulation, endometrial thickness is 12–15 mm and, as progesterone secretion by the corpus luteum increases, endometrial glands begin to secrete their products and the luminal epithelium (the single cell layer that covers the endometrial surface) exhibits transient swellings known as pinopodes. By the seventh day of exposure to elevated progesterone, the endometrium becomes receptive to embryo implantation and remains so for a few days, a period known as the window of implantation or receptive phase.

The success of embryo implantation depends on the quality of the blastocyst (a developmental stage of the zygote able to attach to the endometrium) and on endometrial receptivity. The latter depends on progesterone which, acting through its receptors on an estrogen-primed endometrium, changes the transcription rate of target genes. Hence, endometrial receptivity is associated with either enhanced or decreased expression of certain repertoires of genes in comparison with prereceptive stages of the endometrium. A morphological correlate of this receptivity is the predecidual transformation of the cells surrounding the endometrial blood vessels. The absence of a blastocyst in the mid-luteal phase allows luteolysis (breakdown of the corpus luteum) to proceed and menstruation to start a week later.

The Conceptional Cycle

The cycle in which a pregnancy begins is referred to as the conceptional cycle. In such a cycle, menstruation does not take place 2 weeks after ovulation as it does in an infertile cycle because the corpus luteum does not regress but continues to produce progesterone, thus menstruation does not occur. The conceptional cycle ends normally 9 months later with parturition, followed by lactational amenorrhea until menstrual cyclicity resumes. Ten percent or more of conceptional cycles will end prematurely due to death of the conceptus (developing zygote), the embryo or the fetus, or other causes, but before the product of conception is viable outside the womb. Loss of the embryo or fetus in these circumstances is referred to as abortion (or clinically often as 'miscarriage'). In addition, a variable number of conceptuses (estimated at 20–50%) die during or soon after they implant in the endometrium and menstruation may occur at the normal time or somewhat delayed without the woman being aware of this failed implantation.

The ovarian and endometrial cycles of the menstrual and the conceptional cycles do not differ until after ovulation, except for possible subtle changes in response to sexual intercourse and the presence of seminal plasma components and spermatozoa that interact with the epithelial cells lining the inner surface of the genital tract. The major differences between both cycles, before the delay in menses occurs, take place after ovulation and particularly at the time of implantation and thereafter.

A sequence of several fundamental processes is required for the natural occurrence of a conceptional cycle. The first two events are sexual intercourse and ovulation; the former must be close to, but not after, ovulation. They must be followed by the encounter of the gametes, oocyte, and spermatozoon, usually in the ampullary segment of the Fallopian tube (**Figure 6**), where fertilization takes place leading to the formation of a single cell, the zygote, representing the beginning of a new individual. This is followed by development of the zygote up to the morula stage, its transport to the uterine cavity where it continues to develop up to the blastocyst stage, which is the stage at which it is capable of implanting in the endometrium.

Following fertilization within the ampullary segment of the Fallopian tube, the zygote develops within this organ up to the early morula stage composed of 8–12 cells in the course of 3 days at the end of which it passes into the uterine cavity. In the following 3 days the morula develops into a blastocyst inside the uterus. At the end of this period, the blastocyst expands, loses the zona pellucida, and begins to implant in the endometrium.

Implantation of the blastocyst starts in the middle of the luteal phase when progesterone secretion by the corpus luteum is at its peak. As implantation begins, the trophoblastic cells of the blastocyst begin to secrete increasing amounts of the hormone human chorionic gonadotropin (hCG), which passes into the mother's bloodstream. Acting upon the corpus luteum, hCG prevents its involution and keeps it secreting high levels of progesterone and estradiol. In this manner, the hormonal support of the endometrium is maintained and menstruation is prevented so that the implanted blastocyst can continue its development in the endometrium.

Gamete Encounter and Fertilization

The vast majority of acts of sexual intercourse do not generate a pregnancy in fertile couples who are not

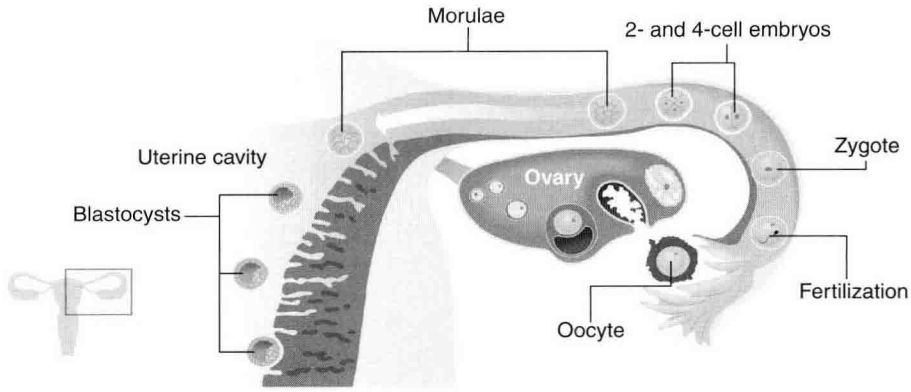

Figure 6 Preimplantation development of the zygote.

using any means to avoid it, indicating that the reproductive process in the human has rather low efficiency in comparison with other domestic and wild species in which almost every mating is followed by pregnancy. There are several reasons for this difference, one of them being that ovulation takes place in one of the 21–35 days of the menstrual cycle and intercourse can occur multiple times randomly distributed along that period and by chance not close enough to ovulation to allow the encounter of fresh gametes. By carefully monitoring the day of ovulation and days of intercourse in 625 cycles of 221 women seeking to become pregnant, Wilcox *et al.* (1995) were able to establish that a single act of sexual intercourse can generate a conceptional cycle if it takes place on the day of ovulation or in any of the 5 preceding days. These six days of the menstrual cycle are designated as the fertile period of the menstrual cycle. The probability of generating a conceptional cycle is highest when intercourse occurs on the last three days of the fertile period, when it is close to 35%. Wilcox *et al.* (1998) also established that 30% of conceptional cycles identified by detection of hCG in the urine ended before the pregnancy was clinically recognized. Since menstruation in such cycles occurs at about the expected time, women are not aware of these early conception losses and perceive the cycle as a normal, nonconceptional menstrual cycle.

Spermatozoa can survive in the genital tract of women and retain their fertilizing potential up to 5 days after intercourse. On the other hand, the oocyte needs to be fertilized within the first few hours after ovulation to generate a viable, healthy zygote with full developmental capacity. This explains why the fertile period is limited to six days asymmetrically distributed relative to the day of ovulation.

Ovulation is preceded by high estradiol and low progesterone levels in the circulation. Therefore, the endocrine milieu prevailing during the fertile period is optimal for the production of abundant, clear, more watery and less viscous cervical mucus that fills the cervical canal and is easily penetrable by spermatozoa.

When a man ejaculates during coitus, semen containing several hundred million spermatozoa is delivered to the vagina. If this occurs during the fertile period, sperm cells will easily pass into cervical mucus extruding from the external opening of the cervical canal. In fact, several hundred thousand spermatozoa will do so within the first hour and most of them will colonize the cervical crypts where they can remain viable for days, forming a sperm reservoir. In a short-lived first phase, some sperm cells are passively transported within minutes to the Fallopian tube while the others actively migrate from the cervical reservoir to the Fallopian tube continuously over the next hours and days. Animal experiments have demonstrated that passively transported sperm do not have the capacity to fertilize and that the fertilizing sperm come from the active phase.

Noncapacitated spermatozoa (not yet ready to fertilize an oocyte) reaching the Fallopian tubes bind for hours to the epithelial cells lining the lumen and subsequently are released in a capacitated state. Capacitated spermatozoa can readily fertilize an oocyte, but they soon lose viability if ovulation has not taken place. Fresh spermatozoa coming from the cervical reservoir can repeat this cycle until ovulation takes place or for a maximum of 5 days after intercourse. Once a capacitated sperm cell penetrates the cumulus oophorus, it binds to the proteinaceous layer covering the oocyte, called zona pellucida. Here it loses part of the outer cell membrane allowing the release of various enzymes (acrosome reaction) that help the sperm drilling a pathway through the zona until it reaches the oocyte cell-membrane. Again, the sperm binds to this membrane and fuses its own membrane with it. The sperm head carrying one set of paternal chromosomes then comes inside the oocyte cytoplasm. Meanwhile, the oocyte undergoes several processes in response to sperm signaling. It releases components (cortical granules) that turn the zona pellucida impenetrable to further spermatozoa, completes the second meiotic division keeping only one half of the maternal chromosomes (haploid condition)