PART

II

Applied Reproductive Science; Contemporary Interventions in STIs/RTIs and HIV/AIDS; Significance of Accessible Contraception Services

CHAPTER

5

Applied Reproductive System: Scientific Aspects

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CHAPTER OBJECTIVES

The main objectives of this chapter are to:

- Provide an overview of human reproductive physiology
- Review current areas of interest and controversy in human reproductive science

Introduction

This chapter reviews key scientific aspects of human reproduction, with particular consideration given to areas that impinge on sexual health and functioning. The focus is upon contemporary issues, concepts, and controversies. Recent research is emphasized, and various academic reviews are noted for the reader who wishes to explore key topics in greater depth. Consulting an adjunct textbook is recommended to the reader who comes to this chapter lacking the essential fundamental knowledge of applied reproductive biology.

The Male Reproductive System

Spermatogenesis

Spermatogenesis, the production of sperm cells, takes place within the coiled seminiferous tubules of the testis. Spermatogonial stem cells divide to produce a prodigious amount of developing sperm cells: the fertile male produces over 2,000 sperm cells per second. The entire process of spermatogenesis, starting with spermatogonial division and concluding with deposition of morphologically complete sperm into the lumen of the coiled seminiferous tubule, takes approximately 10 weeks. These sperm cells are immotile and are conveyed passively to the adjacent ductus epididymis, where they undergo subtle maturation steps required to render them ready for fertilization. Non-ejaculated sperm can be stored in the ductus epididymis for approximately 2–3 weeks. In cases of prolonged abstinence, some storage may also occur in the lower reaches of the vas deferens, to which the ductus epididymis is adjoined. (For reviews and further reading see Carreau, Bouraima-Lelong, & Delalande, 2011; Barratt [1995]; Carreau, Bouraima-Lelong, and Delalande [2011]; Grootegoed et al. [1995]; and Verhoeven [1999].)

Sperm Integrity

The coiled seminiferous tubule is compartmentalized via tight junctions between its composite cells, and is thus to some extent protected from blood-borne cytotoxic and mutagenic molecules. Additionally, there appears to be a particularly high level of mutation repair activity associated with spermatogenesis. Nevertheless, due to the continuous turnover of spermatogonia, sperm cells tend to accumulate mutations as the male ages. Accordingly, a paradigm of elevated risk of transmitting de novo mutations—and hence genetic disorders—to offspring of older men has emerged in recent years. For example, the risk of a 40-year-old man fathering a child with a dominant mutation is approximately the same as the risk of Down syndrome for a child whose mother is 35–40 years. Such paternal age-related mutational risk also applies to polygenic conditions, including autism, schizophrenia, epilepsy, and intellectual disability, with recent literature typically reporting at least a twofold increase in the incidence of such conditions for fathers older than 50 compared with fathers under the age of 30 (Hehir-Kwa et al., 2011; Krishnaswamy et al., 2009; Lynch, 2010; Petersen, Mortensen, & Pedersen, 2011; Reichenberg et al., 2006; Vestergaard, Mork, Madsen, & Olsen, 2005). In this light, a rule on the maximum age for sperm donation

would appear prudent. For example, in the United Kingdom the age limit is presently set at 45 years, and at 40 years in the United States, exceptional circumstances notwithstanding.

In recent years, concerns have been raised that sperm counts and, to a lesser extent, sperm quality may be declining compared with historical values (for examples, see Auger, Kuntsmann, Czyglik, & Jouannet, 1995; Carlsen, Giwercman, Keiding, & Skakkeback, 1992; Sharpe, 2010; Swan, Elkin, & Fenster, 2000). The hypothesis here is that the modern environment may impact negatively upon spermatogenesis and semen parameters. For example, pollutants and alleged endocrine disruptors—including dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyl (PCBs), pesticides, and food additives might exert a subtle toxic effect on testicular cells or other components of the male reproductive tract, especially during fetal development stages (see, for example, Rouiller-Fabre et al., 2009). Lifestyle factors—at least in Westernized nations—such as lack of exercise and obesity might also have a negative impact (Palmer, Bakos, Owens, Setchell, & Lane; Williams et al., 1993). However, data on historical sperm numbers and semen quality extending far enough back in time are sparse and of questionable reliability, making this hypothesis intrinsically difficult to test. Although the issue remains controversial, is seems reasonable to conclude that firm grounds have not been established to support claims that sperm counts or semen quality are in general decline (see for example Bonde, Ramlau-Hamsen, & Olsen, 2011; Olsen, Zhu, & Ramlau-Hansen, 2011; Velde et al., 2010). However, contemporary datasets will prove invaluable for future comparisons between present and future sperm values.

Hormones and Male Reproductive Function

Spermatogenesis is driven by the gonadotrophins follicle stimulating hormone (FSH) and luteinizing hormone (LH). In terms of sex steroid production, LH drives the Leydig cells (located outside the coiled seminiferous tubules) to produce androgens (mainly testosterone). In addition to acting within the coiled seminiferous tubules to drive sperm development, molecules of testosterone enter the bloodstream. Bloodborne testosterone promotes reproductive functionality within the body (e.g., maintenance of sexual morphology) and the brain (e.g., sexual behavior). Testosterone levels are positively correlated with sex drive, with androgen receptors within the brain able to bind and respond to testosterone. However, where testosterone production declines or is eliminated (e.g., iatrogenically), sex drive and male-associated behaviors are not fully eliminated. This apparent paradox is explained by the fact that testosterone acts on the brain during puberty to permanently alter brain function in a masculine direction (see Blakemore, Burnett, & Dahl, 2010; Neave & O'Connor, 2009; Shirtcliff, Dahl, & Pollak, 2009; Sisk & Foster, 2004; Spear, 2000).

Production of Semen

Arousal and ejaculation occur independently of spermatogenesis; the latter operates as a background process, slowly building up reserves of sperm cells. At the peak of sexual excitement, and particularly during mechanical stimulation of the penis, a proportion of these cells are discharged from the epididymis (or lower reaches of the vas deferens) to become mixed with the fluids added by the accessory glands intersecting the tract. This process, termed *emission*, results in the sperm cells becoming suspended in the fluid known as semen (or seminal fluid). The epididymal fluid containing the sperm contributes only about 2% of the volume of semen. Thus, vasectomized men experience no noticeable reduction in the volume of their semen per ejaculate.

The accessory glands that add most of the fluid to form semen are the seminal vesicles (one per vas deferens) and the prostate gland; these structures contract immediately prior to ejaculation to expel their liquid contents. The seminal vesicle provides a thick, mucoid, alkaline fluid making up approximately two-thirds of the semen volume; the prostate secretes a thin, milky, slightly alkaline fluid making up the remaining volume. A typical ejaculate ranges in volume from 2–6 mL, with more frequent ejaculations resulting in diminished volume, and abstinence resulting in higher volumes. Sperm density is typically 100 million sperm per milliliter of semen; levels below 20 million/mL generally equate with substantially impaired fertility, indicating the need for many sperm cells to achieve fertilization. Semen contains a wide mix of molecules, including agents to control the viscosity of the ejaculate, cathelicidins to combat infection, prostaglandins that induce uterine contractions in the recipient female, and a range other molecules, including hormones and growth factors, the functions of which are not fully understood.

Commencing in the early stages of sexual arousal, and continuing until the moment of ejaculation, the paired bulbourethral glands steadily secrete an alkaline fluid into the urethra. This fluid, known as the pre-ejaculate, functions to reduce acidity in the penis (sperm being unable to tolerate low pH environments), and to lubricate the bulbous tip of the penis (the glans penis) to permit foreskin retraction and facilitate vaginal entry. Quantities of pre-ejaculate produced appear to vary significantly and consistently among individual men, reflecting different genetic backgrounds. An important question in the context of human reproductive health is whether the pre-ejaculate contains sperm cells. If so, this would have important implications for sexual behavior, as pregnancy could result in the absence of ejaculation (for example, where a condom was used only immediately prior to ejaculation—a fairly common behavior). Certainly, the standard advice has been that barrier methods of contraception should be deployed prior to any penetrative sexual contact—and of course this advice cannot be faulted for erring on the side of caution, or in terms of avoiding sexually transmitted infections (STIs). However, the numbers of sperm empirically discovered in pre-ejaculatory fluid have been low (Killick, Leary, Trussell, & Guthrie, 2011; Zukerman, Weiss, & Orvieto, 2003), and it thus seems unlikely that pregnancy could arise merely from pre-ejaculatory fluid.

Ejaculation

At the height of sexual arousal, immediately prior to ejaculation, the sperm and fluid contents are mixed and moved along the vasa deferensia by smooth muscle contractions. At this moment, the internal urethral sphincter contracts to avoid retrograde ejaculation (i.e., semen entering the bladder). Ejaculation itself—the expulsion of semen from the penis—is powered mainly by the skeletal musculature associated with the penis. The relevant muscle pairs are located within the abdomen close to the base of the penis and wrapped around the base of the penis. Neurological or muscular conditions can lead to ejaculatory dysfunction, where the penile musculature is unable to forcefully contract to expel the semen, and/or to internal emission problems where the smooth muscle is similarly unable to contract adequately or in a properly coordinated manner.

Semen and Female Immunological Response

Beyond its function as a medium for sperm delivery, there is evidence that semen may contain factors that have physiological effects on the female's body. One such effect is the possible "conditioning" of the female's immune response so as to tolerate the potentially antigenic molecules contributed by the male partner. Following ejaculation, the immune system responds to the presence of foreign proteins from the male (in semen and on the sperm cell surface) in a number of ways, including increased macrophage activity. It is, however, essential that this immune response within the female tract is kept in check, otherwise fertilization would be impossible due to sperm cell destruction; or, if a conceptus was formed, pregnancy would be terminated by immunological attack on the embryo, fetus, or placenta due to the recognition of foreign proteins on the cells of these entities. (The potential of the female tract to react vigorously toward her partner's antigens is evidenced by rare cases of women who are allergic to semen, in whom the result of unprotected sex is severe inflammation of the vulva/vagina, with the possibility of anaphylactic shock.) Normal fertilization and pregnancy is associated with a special immunological tolerance toward potentially antigenic male-contributed proteins. The details of this tolerance have not yet been fully explained; however, there is some evidence that exposure to the semen of one partner may serve as a trigger for immune toleration of proteins from that same male. Indirect evidence comes from the epidemiological observation that preeclampsia, a serious disorder of gestation characterized by proteinuria and high blood pressure, is more common when pregnancy results from a male with whom the woman has not had frequent pre-conception unprotected coitus. Thus, unprotected sex appears to promote immunological tolerance, and the mechanism is triggered by semen exposure (for example, see Sadat, Kalahroudi, and Saberi, 2012). Indeed, this acquired tolerance may be most strongly promoted not by vaginal intercourse but by oral sex (fellatio), especially where the semen is swallowed, suggesting a possible biological role for this sexual practice (Koelman et al., 2000). The male factors assumed responsible for triggering female immunological tolerance to male-contributed antigens appear to be secreted from the prostate gland and seminal vesicle. Candidate factors include transforming growth factor beta (TGF-beta) and other cytokines. These agents are envisaged to interact with the epithelial cells of the lower reaches of the female tract, resulting in activation of cytokines and immune cells that serve to regulate and suppress the potential immune response against male-derived antigens, thus facilitating sperm survival, fertilization and gestation. (See reviews by Robertson [2005], and Rodriguez-Martinez, Kvist, Ernerudh, Sanz, and Calvete [2011].)

Does Semen Play a Role in Mental State?

Several components of semen, including testosterone, estrogen, and prostaglandins, are absorbed through the vaginal epithelium and can be detected in the bloodstream within a few hours of ejaculation, which has led some researchers to hypothesize that these seminal fluid components may have an effect on the mental state of recipient women (Ney, 1986). One study examined this hypothesis among a sample of 293 sexually active college females, condoms usage serving as a proxy for the presence or absence of semen in the reproductive tract, and such usage being compared with depressive symptoms (via the Beck Depression Inventory). Unprotected sex was found to correlate with low depression scores. Among those who used condoms inconsistently, the frequency of condom usage positively correlated with depressive symptoms (Gallup, Burch, & Platek, 2002). Thus, increased exposure to semen appears to correlate with reduced depressive symptoms. However, an alternative explanation exists, namely that females who choose to engage in unprotected sex are either happier with their partners than their condom-using counterparts, or are less depressed for other reasons (e.g., dispositional), with this mental state being the impetus for unprotected sex, as opposed to the converse. Moreover, the Gallup et al. study does not appear to have been replicated and, although interesting and potentially of significant importance in the context of human health, the notion that semen may biochemically alter the recipient's mood remains unproven at present.

The Penis

The penis is composed of erectile tissue sheathed in strong elastic skin. The erect penile tip takes the form of an enlarged glans penis, of significantly greater width than the penile shaft. It has been hypothesized that the glans penis has a protective action during coitus, with the role of absorbing the considerable forces associated with intromission. In a unique and elegant study, Hatzichristou et al. (2003) examined this hypothesis using five volunteer patients scheduled for surgical removal of the glans penis (due to penile carcinoma). During surgery, intrapenile pressure

was increased by pumping saline into the erectile tissues, external compressive forces were delivered to the penis effectively mimicking the rigors of coitus, and the resultant pressure changes were recorded. Intrapenile pressures were higher following removal of the glans penis, indicating that the glans penis serves to reduce such pressures during sexual intercourse. Moreover, two of the patients' partners reported pain during sex post-operatively, probably due to the "ramming" action of the end of the rigid shaft of the penis into the vaginal wall, unprotected by the glans penis, suggesting that the protective role of the glans penis during coitus applies to the female as well as to the male (Hatzichristou et al., 2003).

The glans penis has the ability to displace semen out of the vagina by pumping it back along the outside of the penile shaft, as discussed later in this chapter in the context of sperm competition. Such semen removal is contrary to the biological goal of maximizing the likelihood of fertilization, and would thus appear to be maladaptive. It is not so, however, because immediately following ejaculation the penis loses turgor and the glans penis accordingly reduces in size: thus, following ejaculation, penile thrusting does not contribute to sperm loss.

Penile size is notoriously an area of concern among men. Although a number of studies have attempted to establish datasets on penile size, many reports are unreliable due to probable misreporting of sizes by participants, which may be a factor of poor study design. Better quality studies have generally reported an average flaccid length of approximately 3.5 cm and an average erect length of approximately 14.5 cm, with most men being within the range 13–16 cm (Khan, Somani, Lam, & Donat, 2012; Mondaini et al., 2002). Such data are important for a number of purposes, including facilitating clinical reassurance of anxious males as to the normalcy of their penile endowment. Clinical application of such data may relate to counselling in urology and for the purposes of reconstructive surgery; for example, in cases where penile augmentation may be deemed medically necessary or appropriate. Therefore, such data is considered useful before planning any medical/surgical interventions for penile size (see Dillon, Chama, & Honig, 2008).

Erection

Although the processes of erection and ejaculation are closely related during sexual intercourse, ejaculation can occur in the absence of erection. Indeed, each of these sexual responses can exist without the other. Thus, despite their association during coitus, erection and ejaculation are distinct physiological processes. Common to both erection and ejaculation, the pelvic nerve plexus serves as a junction for neural input to the anatomic structures involved. Brain regions that control erection and ejaculation via the spinal cord are part of a larger brain network that regulates overall sexual response. The neurotransmitters dopamine and serotonin both play key roles in the control of erection and ejaculation (see Giuliano, 2011).

At a physical level, penile erection is a hydraulic process. It commences when the arterioles of the penis dilate, allowing a net inflow of blood into the spongiform tissues of the penis, and rigidity increases as expansion of the internal tissues compresses the venous return and thus reduces blood outflow. Arteriole dilation is a consequence of nervous stimulation: sexual arousal (via the brain) and direct sexual contact (locally to the genitalia) lead to the production of cyclic guanosine monophosphate (cGMP) molecules, which in turn act as a signal to the arterioles to induce vasodilation. Nervous stimulation must not cease, because cGMP is continually being broken down by cGMP phosphodiesterase, an enzyme that is always present. A lack of sufficient nervous stimulation will thus lead to failure to produce or maintain an erection; that is, impotence or erectile dysfunction (ED). In the past, ED was frequently treated by injection of a vasodilator into the base of the penis. Such treatment is effective but inconvenient; not only is an injection required, but the resultant erection is immediate and will generally not abate for several hours. Thus, in the past, ED was traded for priapism. In recent years, oral cGMP phosphodiesterase agonists such as sildenafil (Viagra) have become available and have revolutionized the treatment of ED. By inhibiting cGMP phosphodiesterase and thus preventing the breakdown of cGMP, vasodilation and hence erection is facilitated. Unlike the older vasodilator approach, erection is not initiated by the drug treatment alone; sexual excitement is required in order to drive the production of cGMP via nervous stimulation—thus avoiding unwanted erections in inappropriate contexts. Moreover, these new agents are associated with minimal adverse effects (see an interesting review by Tsertsvadze et al., 2009).

The Female Reproductive System

Oogenesis

Prior to ovulation, oocytes are contained within ovarian follicles (one oocyte per follicle). During prenatal life, thousands of primordial follicles are produced, such that the fetal ovary contains over 3 million follicles at its peak. Thereafter, a process of follicular self-destruction, known as atresia, results in the loss of most of these follicles. This process continues throughout the woman's life until the ovary contains no functional follicles, at the time of menopause. Atresia is characterized by the initial development of a small subset of follicles (at a rate of 10–15 follicles per day); prior to puberty all of these follicles fail to develop fully and are lost. During the reproductive years, one follicle per ovarian (monthly) cycle develops fully, resulting in ovulation of a single oocyte. The process of follicular development is under the control of FSH: extra FSH (either for clinical reasons or due to superovulation associated with in vitro fertility [IVF] procedures) results in more than one follicle reaching maturity. Beyond being a mechanism to control numbers of

oocytes ovulated, atresia may function as a means to select for the "best" follicles/oocytes. However, this is somewhat speculative, and no clear evidence of a mechanistic basis for such a selection effect exists. Additionally, the surviving oocytes do not represent a perfectly functional population; thus, if such active selection is indeed occurring, it is an imperfect process. The precise factors that control atresia are yet to be explained, and the mechanistic details of follicle/oocyte recruitment and apoptosis presently remain an enigma. (For useful reviews, see Hartshorne , Lyrakou, Hamoda, Oloto, & Ghafari [2009]; Krysko et al. [2008]; and Gougeon [2010]).

The Ovarian Cycle

Although each ovarian cycle lasts (on average) 28 days, the primordial follicle that becomes the ovulatory follicle will have started its maturation several months prior. The exact initiation of follicular maturation is intrinsically difficult to pinpoint, given the microscopic size of primordial follicles and the subtle nature of early changes; thus, it remains unclear as to how long the entire process of oocyte maturation takes. Approximately 3 months prior to ovulation, primordial follicles reach the early antral stage, in which fluid accumulation within the follicle results in a marked increase in size. By day 1–5 of the ovarian cycle, approximately 5 antral follicles exist, one of which will become the dominant (pre-ovulatory) follicle. At 20–25 mm in diameter, this follicle is much larger than its primordial predecessor. The size increase is due to fluid accumulation and multiplication of constituent cells. Ovulation, which typically occurs in most women at a relatively constant 14 ± 2 days prior to the onset of menstrual bleeding, sees the oocyte being released through the ovary wall and into the fimbriated opening (ostium) of the oviduct. Thereafter, the constituent cells of the ruptured follicle undergo dramatic changes as the "damaged" ovarian site is revascularized and remodeled. The overall effect of these changes is to convert the follicle into a corpus luteum, a structure responsible for sex steroid biosynthesis. The corpus luteum develops until approximately midway through the post-ovulatory phase, whereupon it declines, eventually to become the corpus albicans, an inactive structure (**Figure 5-1**).

Hormonal Aspects of Female Reproduction

As mentioned above, follicular/oocyte development is driven by the gonadotrophin FSH. Ovulation is triggered by a surge of the gonadotrophin LH. An additional crucial role for LH is to stimulate the follicular cells such that estradiol and other estrogenic hormones (henceforth referred to collectively as "estrogen") are produced from the ovary. Specifically, LH drives the theca cells (located in the outer region of the follicle) to produce androgens (mainly androstenedione and testosterone), which are then converted to estrogen by the granulosa cells (located in the inner region of the follicle and contacting the oocyte). In addition to acting within the follicle to drive follicular and oocyte development, molecules of estrogen and (non-converted) androgen enter the bloodstream. These blood-borne sex steroids promote reproductive functionality within the body (e.g., maintenance of sexual morphology) and the brain (e.g., sexual behavior). Following ovulation, the corpus luteum produces progesterone, the main function of which (in the non-pregnant woman) is to promote the final maturation of the endometrium in readiness for possible embryo implantation.

The gonadotrophins are released from the anterior pituitary gland in response to stimulation by gonadotrophin releasing hormone (GnRH). The hypothalamus is the source of GnRH, which is released in a pulsatile manner approximately once per hour. Estrogen acts as an inhibitor of GnRH and gonadotrophin release, and the gonadotrophins act on the anterior pituitary to inhibit their own release. Thus, the hormonal axis controlling estrogen production is under negative feedback regulation. However, it is important to note that the hypothalamus is under the control of the brain, and therefore it is mechanistically plausible that mental state may subtly alter GnRH levels, with such alterations thereby affecting levels of the gonadotrophins and sex steroid levels, and thus potentially altering reproductive functioning. For example, in recent years it has become apparent that positive social events (e.g., success in a competitive situation) lead to slightly elevated sex steroid levels, whereas negative events (e.g., failure, reduction in social status) lead to the converse (see, for example, Eisenegger, Haushofer, & Fehr, 2011; Salvador, 2012) Thus, it is possible that environmental cues, mediated through the brain, may alter reproductive functioning. This may help to explain several common observations in the context of reproductive and sexual medical practice, including that reduced fecundity and lack of sexual desire are associated with depression and stress (Campagne, 2006; Li et al., 2011).

The Female Tract During Coitus

From the perspective of fertilization, the preovulatory and periovulatory phases are the crucial times when the female tract functions to facilitate the delivery of sperm to the oocyte. Estrogen stimulation is largely responsible for this functionality. During the preovulatory phase, estrogen levels rise sharply, due to increased secretion from the increasingly developed antral follicles. Sexual arousal during this phase results in the production of vaginal fluid, which functions to lubricate the passageway for the penis. This fluid is the result of exudate from the mucous membrane lining of the vagina and secretion from the Bartholin's glands (greater vestibular glands) lying close to the outer opening of the vagina. The Bartholin's glands are histologically similar to the bulbourethral glands in the male, and arise from the same fetal tissue.

The Physiology of Female Sexual Arousal

Sexual pleasure is of great importance in human sexuality, and the underlying physiological structures and functions

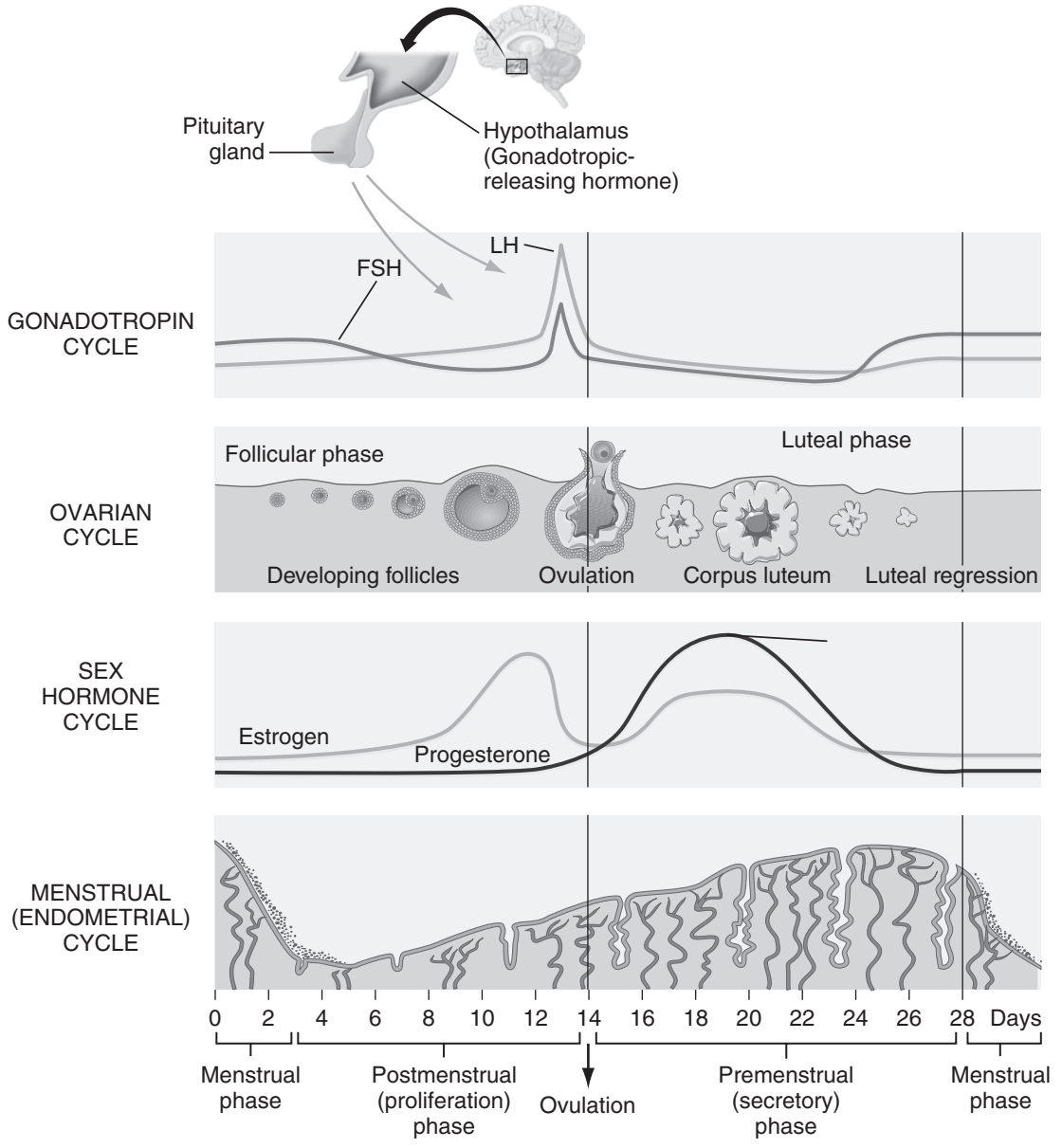

Figure 5-1 Menstrual Cycle: Interconnected Impact of Ovarian, Endometrial, and Pituitary Cycles (Phases of Hormonal Fluctuations and Structural Changes Numbered in Sequence)

are of significant interest. Some aspects in this context remain highly controversial: for example, the existence (or otherwise) of the so-called G-spot, and its anatomy. Other aspects have arguably been underresearched: for example, the anatomy and physiology of the clitoris. Modern imaging technologies, including MRI and ultrasound, have revealed new insights into female sexual anatomy (O'Connell, Sanjeevan, & Hutson, 2005; Puppo, 2011), and the physiology of arousal and penetration. For example, in one recent study ultrasound was performed during coitus, with the female volunteer in the gynecologic position while her partner penetrated her from a standing position. The resultant ultrasound images indicated that the root of the clitoris has a very close relationship with the anterior vaginal wall, with both entities being activated as a single anatomical and functional unit during thrusting by the penetrating penis. This anatomic relationship might explain the pleasurable sensations associated with the anterior vaginal area, the so-called G-spot (Buisson , Foldes, Jannini, & Mimoun, 2010). Such studies represent the initial phase of a new pathway of research that may reveal fascinating insights into female structure and function during sexual arousal and coitus.

Female Orgasm: Functional?

It has not been reliably demonstrated that female sexual excitement and orgasm have an enhancing effect on fertility, and skepticism surrounds such claims (Levin, 2011). Specific adaptations exist that are suggestive of such a role for female excitement/orgasm, although it is possible that these are vestigial functions only—that is, they may have evolved as

adaptations in our pre-human ancestors but now have no clear effects and will eventually be removed by natural selection. As mentioned in the previous section, real-time studies of coitus in human subjects using MRI and ultrasound have cast light on the physical changes within the female tract when coitus occurs (Buisson et al., 2010; Faix, Lapray, Callede, Maubon, & Lanfrey, 2002; Faix, Lapray, Courtieu, Maubon, & Lanfrey, 2001; Schulz, van Andel, Sabelis, & Mooyaart, 1999). In respect of female orgasm, interpretations of such images have suggested that, as orgasm is approached, the cervical region lifts upward and the cervix itself simultaneously dips down towards the tip of the penis, in a process described as "tenting." However, few such studies have been conducted, and it is therefore difficult to draw firm conclusions about whether and to what extent physical changes in the vagina/cervix associated with arousal and orgasm occur to enhance sperm uptake. Issues concerning (1) a possible functional role in terms of enhancing fertilization and (2) its evolutionary origins, have rendered the female orgasm a topic of intense debate among reproductive biologists. Beyond increasing the probability of fertilization from a given instance of coitus, if female orgasm does have a facilitative role in fertilization this may have important implications in terms of "sperm selection." These aspects are discussed later in this chapter.

Semen in the Female Tract

Following ejaculation, substrate proteins from the seminal vesicle are rapidly acted upon by coagulation-promoting enzyme molecules from the prostate gland, such that the liquid semen is coagulated into a gel (coagulum) (Lilja, Oldbring, Rannevik, and Laurell, 1987). The coagulum is hydrophilic and avidly adheres to the vagina and cervix, thus reducing sperm loss through leakage out of the vagina. However, sperm are mechanically trapped and immotile within the gel by binding to semenogelin molecules from the seminal vesicle and zinc ions from the prostate. Trapped sperm must be freed in order to swim into the cervix; slow-acting enzyme molecules from the prostate facilitate this by breaking down the gel matrix (Lilja & Laurell, 1984). This liquefaction process occurs over a period of minutes to more than 1 hour. Individual males exhibit markedly divergent durations of semen coagulation-liquefaction, and sexual behavior (e.g., frequency of ejaculation) causes intra-individual variations in the process (Amelar, 1962; Dunn & Picologlou, 1977).

Cervical Functions Following Sperm Deposition

The cervix sits at the top of the vagina, and is the main site of deposition for semen; hence, this structure is exposed to high numbers of sperm. During the postovulatory phase, due to the presence of high levels of progesterone (secreted by the corpus luteum), the cervical fluid becomes thick, fibrous, and inhospitable to sperm. By contrast, the preovulatory and periovulatory cervix produces a thin, stretchy, highly hydrated fluid in which sperm may swim and thrive. As soon as ejaculation occurs, sperm begin to transit this cervical fluid and enter the uterus; however, many sperm do not immediately pass through the cervical os, and instead become localized in microscopic crypts in the cervical wall. The details of what happens to such sperm en route to the oocyte have been gleaned predominantly from animal studies, and it remains unclear as to what precisely occurs in humans. However, the following descriptive model may be constructed from the available data: sperm within the cervical crypts lose motility and form attachments between their head regions and the crypt surface. Thereafter, at varying periods ranging from minutes to hours or even days, sperm detach from the crypt wall, regain motility and traverse the cervical os to continue their journey toward the upper reaches of the tract. In keeping with this model, the presence of viable sperm has been detected in human cervical fluid up to 5 days post-insemination (Gould, Overstreet, & Hanson, 1984; Mortimer, 1994). Thus, around the time of ovulation, the cervix appears to function as a steady-release mechanism to ensure that relatively steady numbers of sperm reach the ampulla of the oviduct (the site of fertilization) over a protracted period. The benefits of this are likely to be twofold: to maximize the likelihood of fertilization by ensuring that sperm will be present when the oocyte enters the scene, and to ensure that the numbers of sperm reaching the oocyte are low enough to reduce the risk of polyspermy to acceptable levels.

The Role of the Uterus and Oviducts in Sperm Transport

Sperm reaching the oviduct appear to be helped on their journey toward the oocyte by mild peristaltic-like contractions of the uterus. Following estrogen stimulation, and in the absence of progesterone, the myometrium is rendered contractile, and prostaglandins within semen (originating from the seminal vesicles) promote this contractility. Specifically, the prostaglandins appear to promote contraction of the upper part of the uterus at the uterotubular junction, resulting in a negative pressure in the uterus and a mild pumping action of the uterine wall, thus drawing sperm upward into the oviduct (Bygdeman, Gottlieb, Svanborg, & Swahn, 1987; et al., 1987; Karim & Hillier, 1975). Work using modern imaging techniques including sonography has shed further light on this uterine contractility process. Using such techniques, Zervomanolakis et al. (2007) examined the function of the uterus and oviducts to determine whether these structures acted as a sperm pump. Labeled particles (to mimic sperm) were introduced to the vagina during the preovulatory phase and were observed to enter the uterus and oviducts, apparently propelled by peristalsis-like contractions, with the greatest number of particles being directed to the oviduct associated with the ovary containing the mature follicle. Given that such particles were non-motile (unlike sperm), this provides good evidence that the female tract is able to actively

pump vaginal contents upward and toward the oocyte. Interestingly, an increase in peristaltic contractions was observed following the administration oxytocin, a hormone associated with female sexual arousal (Zervomanolakis et al., 2007). However, the extent to which such uterine responses may be facilitative for fertilization remains unclear, and more research in this area would be beneficial.

The uterotubular junction functions as an intermittent sphincter, allowing or preventing sperm from accessing the oviduct. Once within the initial region of the oviduct (the isthmus), sperm may form transient attachments with the smooth epithelial lining of the duct, at which point motility is reduced. As with the abovementioned events at the cervix, this process of attachment/slowing may function to maximize steady-stream delivery of sperm to the ampulla, with "dormant" sperm residing in the extensive epithelial folds—although again, much of this perspective has been gained from animal studies, and human details remain to be validated. However, the oviduct is conceptually a very attractive site as a potential storage depot for sperm: in contrast to the lower reaches of the tract (uterus, cervix, vagina), where leukocytes accumulate post-coitus and attack sperm cells (quite possibly including undamaged sperm cells), the oviduct environment is convivial to sperm (Murray & Smith, 1997). It has not been determined with certainty how long human sperm can remain viable within the female reproductive tract. In fact, there may be no single duration figure possible, because genetic and environmental factors affecting both men and women undoubtedly lead to variance in the duration of viable occupation. However, in vitro studies of sperm suggest that 5 days is not unrealistic for sperm deposited shortly prior to ovulation, a number that is supported by research involving human participants (Wilcox, Weinberg, & Baird, 1995). These stored sperm must reside somewhere within the tract, and the isthmus of the oviduct is currently accepted as the most promising reservoir.

Sperm become fully capacitated within the oviduct, due to signaling factors present within the oviduct fluid. Capacitated sperm swim vigorously (a transiently reversible phenomenon known as hyperactivation), bind with the oocyte, and undergo the acrosome reaction, in which enzymes are released from the sperm to facilitate entry into the oocyte. If an oocyte is present in the ampulla, sperm in this region hone in on the oocyte, clearly being attracted to it. The precise nature of the mechanism of attraction remains to be fully elucidated, but appears to involve sensing by the sperm of the subtle temperature gradient (of approximately 2°C) along the oviduct and a chemotactic agent(s) released from the egg. (For a very useful review, see Suarez and Pacey, 2006.)

Sperm Selection in the Female Tract

The current view among most reproductive physiologists, derived from experimental and clinical observations, is that only a small proportion of sperm from the millions ejaculated into the vagina will reach the oviduct (Baker & Bellis, 1993). A typical ejaculate contains around 350 million sperm; numbers of sperm appearing in the oviduct (at around the time of ovulation) in the subsequent hours following ejaculation vary greatly (Williams et al., 1993), but it is likely that the oocyte will typically be exposed to only 200–300 sperm. For a given sperm cell to have any chance of achieving fertilization, it must be healthy enough to traverse the various physical, chemical, and immunological obstacles present throughout the female reproductive tract, from vagina to ampulla (see Foo & Lim, 2008). Moreover, to be successful, a given sperm cell must be on a par, or better than, the millions of other co-ejaculated sperm, in terms of swimming and survival ability. Thus, there exists a *de facto* process of sperm selection, with the "fittest" sperm being most likely to achieve fertilization. Presumably there are adaptive benefits to such selection, in that a weak sperm may also be one that is harboring a genetic defect such as a gross chromosomal aberration or a genetic deficit affecting the process of spermatogenesis. Moreover, there is some evidence that the cervical mucus may act as a barrier to sperm carrying structural genetic abnormalities. Bianchi et al. (2004) carried out in vitro experiments on human cervical mucus to determine whether the mucus can act as a mechanism for the removal of sperm that, despite being morphologically normal, contained chromatin abnormalities. The results obtained indicated that sperm containing higher levels of some forms of DNA structural damage are more likely to be retained by the cervical mucus barrier (Bianchi et al., 2004). Sperm selection within the female tract should act such that, from a mixture of defect-carrying and normal sperm within one ejaculate, fertilization is more likely from the latter sperm. It should also reduce the chances that defects of spermatogenesis are inherited. However, the fact that various genetic defects are frequently transmitted paternally indicates that such selection is far from perfect. Indeed, in many or most cases, genetic defects of a non-structural nature carried by sperm should have no deleterious effects on sperm performance in the female reproductive tract.

Sperm Competition?

Anthropologically, although human reproduction is characterized by lifelong or serial monogamy, the occurrence of extraneous sexual intercourse occurs at a sufficiently high frequency such as to ensure its evolutionary importance. Research surveys have supported this notion. For example, in one study approximately 25% of female college students acknowledged non-monogamy, with approximately one in eight admitting to having sex with two or more males in a 24-hour period (Gallup, Burch, & Mitchell, 2006). Thus, behavioral adaptations may have evolved for males to increase assurance that their genes are indeed the ones transmitted to their chosen (female) partner. However, there is no research to cite in support of this point.

Extrapair Coupling: The Role of Sperm Fitness and Numbers

An additional physiological line of defense may work to assure positive sperm selection. The passive form of sperm selection described would also operate in instances where sperm from two different males came to occupy the same woman's reproductive tract. Suppose a given women has sex with her usual partner on day 12 of her ovarian cycle, and then on day 13 has sex with an extraneous partner. In this case, sperm from both males will be simultaneously present within the woman's reproductive tract, and the sperm from each male is likely to be similarly viable. In such a case, the male who produced sperm of greater "fitness," or in greater numbers, would be more likely to be reproductively successful, in terms of achieving fertilization.

Sperm are the product of intense selection for sperm fitness, and it is therefore unlikely that the outcome of competition between sperm from different healthy partners will generally depend on physiological differences between their sperm. A greater number of sperm would provide a definitive competitive advantage, and non-human primate species that practice frequent polygamy generally have a larger testicular weight (as a percentage of body weight) than do more monogamous primates (Harcourt, Purvis, & Liles, 1995). However, within-species selection for large testes would be strongly moderated by the costs to fitness imposed by maintaining large gonads, especially in view of the high metabolic demands of testicular tissue. In keeping with this evolutionary concept, empirical analysis of human testicular volume (or weight) has demonstrated that, although testis size does positively correlate with the number of sperm ejaculated, there is no evidence of a correlation between testis size and tendency to engage in polygamous sexual behavior (Simmons, Firman, Rhodes, & Peters, 2004).

Physical Removal of Sperm?

In instances where extraneous intercourse had recently occurred, it would be beneficial to the main partner if semen from the extrapair mating were to be removed. In this respect, it has been proposed that the human penis may be structured such as to maximize the displacement of previously deposited semen from the vagina. Results obtained by simulated coitus using artificial penis and vagina models appear to support this contention, and indicate that the coronal ridge (at the base of the glans penis) is the most important morphological feature mediating semen displacement (Gallup et al., 2003). Additionally, sexual behavior may be adjusted as an unconscious means to displace prior semen, and survey-based research has generated findings compatible with this notion. For example, couples who had periods of separation, during which the female partner engaged in extraneous intercourse, often resulted in deeper and more vigorous penile thrusting during subsequent coitus (Gallup et al., 2003; Goetz et al., 2005). However, this field of research is presently limited to a small number of studies, and further research would be required before semen displacement could be accepted as a significant factor in human sperm competition.

Female-Mediated Sperm Flowback and Retention

Another possible form of sperm competition would be active selection of one partner's sperm over the sperm of another partner. For example, in an extrapair coupling with a male of high genetic quality, it would be evolutionarily advantageous to the female if this mate's sperm fertilized her oocyte while her main partner (of lower genetic quality but of proven utility for providing support) brings up the resultant child. Given the aforementioned functionalities of the female tract in terms of storing sperm and preventing or facilitating their journey toward the oocyte, the intriguing possibility exists that the female might be able to (unconsciously) influence the fate of sperm deposited by different males. It would presumably be mechanistically difficult or impossible for the female reproductive tract to differentiate between the sperm of two males when the sperm populations were mixed within her tract. The only plausible way in which the female physiology might be able to select for one set of sperm over another would be to facilitate, or hamper, individual deposits of sperm. In a landmark study using human volunteers, Baker and Bellis (1993) examined sperm loss from the vagina, a process termed *flowback*. They found that flowback occurred in the majority of copulations, with an average of approximately one-third of ejaculated sperm eliminated within 30 minutes following ejaculation. However, in around 1 in 10 copulations, virtually all the sperm were lost through flowback. Sperm appeared to be lost at a lower extent where the woman had experienced an orgasm within 1 minute of the time of ejaculation, suggesting a possible role for female orgasm in sperm retention. The authors proposed the existence of a blow-suck mechanism able to transport the upper vaginal contents into the cervix. Based on the assumption that infidelity is generally associated with a higher rate of orgasm (see Brody, Klapilova, K., & Krejcová, L. 2013; Ellsworth & Bailey, 2013), the implication is that extrapair matings—potentially with genetically desirable males—result in greater sperm uptake and hence a greater probability that the non-partner male fathers a child on whom resources will be expended by the main partner, whose sperm will be subject to a greater degree of flowback (Baker & Bellis, 1993). However, the Baker and Bellis study was of a small scale and does not appear to have been replicated, perhaps due to the intrinsic difficulty of recruiting subjects willing to participate in copulatory experiments involving semen collection, and a great deal of further data on flowback would be required to determine whether the hypothesis of female-mediated sperm selection is valid.

Female Orgasm: Functional Role in Sperm Selection?

Genetically desirable male features include high morphological symmetry (for example, symmetrical facial features). As mentioned earlier in this chapter, it is possible that the female orgasm has a physiological role in facilitating sperm transport and hence maximizing the likelihood of fertilization. Accordingly, the proportion of copulations that are accompanied by female orgasm should positively correlate with the male partner's morphological symmetry. This predicted correlation has been investigated empirically. For example, a questionnaire-based study of 86 sexually active heterosexual couples revealed that women with high-symmetry partners had significantly more (copulatory) female orgasms than did women with partners possessing low symmetry (Thornhill, Gangestad, & Comer, 1995). Subsequent research replicates and supports these findings. For example, in a 2000 study, self-report data from 388 women indicated that women copulating with more attractive men were more likely to experience orgasm than were women who copulated with less attractive men, a correlation that remained significant after statistically controlling for potentially confounding variables (Shackelford et al., 2000). A more recent study explored correlations between female orgasm and various potential markers of male genetic quality, including facial symmetry, and found that more frequent and earlier-timed orgasms occurred in women who copulated with men of apparent high genetic quality (Puts, Welling, Burriss, & Dawood, 2012).

In the context of the apparent correlation between female orgasm and male genetic quality, and in light of the foregoing work on sperm retention by the female reproductive tract, it would be of value to determine whether there is indeed a biological role for the female orgasm in terms of enhancing the likelihood of fertilization. Such a role would be reflective of evolution, in terms of orgasm being an adaptive physiological response. The alternative explanation is that female orgasm is not adaptive but rather has been maintained through evolution simply as a by-product of natural selection on the male physiological apparatus of orgasm associated with ejaculation. These adaptive versus "by-product" explanations have been the subject of vigorous scientific debate. Neither position has been fully tested to date; however, data have emerged that promise to move the debate forward. Zietsch and Santtila (2011) tested one of the central tenets of the by-product explanation, namely that selection pressure on the male orgasm should be transferred to the female genetically, resulting in a positive correlation for orgasmic function in closely related individuals. A questionnaire approach was employed, involving over 10,000 twins and siblings, to examine susceptibility to female orgasm. Significant genetic variation was found for both male and female tendency to orgasm (for a given stimulatory level), as would be expected; however, the researchers found no significant correlation for orgasmic tendency between opposite-sex twins and siblings. This suggests that separate genetic mechanisms control orgasmic tendency/function in males and females. Therefore, it does not appear that female orgasmic function is strongly co-selected with that of the male, thus challenging the by-product explanation for female orgasm (Zietsch & Santtila, 2011). The notion of female orgasm as being a separate functional entity from the male counterpart is given further support from research that has suggested the female orgasm is a more complex entity than that of the male, and may occur in different forms. For example, King and colleagues reanalyzed historical data on female orgasm and identified four orgasm types from descriptions by over 500 women of their orgasms (King, Belsky, Mah, & Binik, 2011).

Somewhat more contentiously, claims have been made that pleiotropic markers of female orgasm functionality are manifested in measurable female phenotypic traits not directly or obviously connected to reproductive physiology. For example, a survey involving 258 women found a correlation between vaginal orgasm and the prominence of the tubercle of their upper lip (Brody & Costa, 2011). However, such findings would need to be replicated before being fully accepted, due to the inevitable potential presence of survey bias (e.g., the sharpshooter fallacy) associated with isolated correlation surveys of this nature. Moreover, the concept of "vaginal orgasm" is not accepted by most experts in human anatomy (Puppo, 2011).

The claims for a functional, adaptive role for female orgasm in terms of sperm selection are countered by two points. First, although suggestive evidence to support this hypothesis does exist (as discussed), the evidence is mostly indirect and is not of a particularly extensive nature. Second, physiological evidence is either lacking, or may actually serve toward refuting the hypothesis. A particular meta-analysis is of interest here: Levin (2011) examined academic articles relating to sperm transport and function in the human female genital tract in the absence and presence of arousal to orgasm. The conclusion was that the majority of reported evidence indicates that the female orgasm has little or no effective role in the transport of sperm in natural human coitus (Levin, 2011).

Sperm Competition and Hormonal Contraception

There is a limited but growing body of evidence that men and women demonstrate changes in their choice of mate according to the phase of the menstrual cycle. At around the time of ovulation, women tend to display a stronger preference for symmetrical, more masculine and less related men. Ovulating women appear to be more attractive to men, probably through physiological by-products of high estrogen stimulation (as opposed to unconscious female signaling). These cyclical alterations in mate preference are presumably the outcomes of evolutionary pressures, and thus are likely to provide reproductive advantages, in terms of maximizing the chances of ideal mate selection (Gangestad & Thornhill, 2008). Hormonal contraceptives (e.g., the combined contraceptive pill) effectively prevent ovulation and the associated hormonal fluctuations. Evidence has emerged that, by removing the periovulatory change in

preferences, hormonal contraception may significantly alter mate choice in both males and females. If this is correct, use of hormonal contraceptives may be associated with altered biological and relationship outcomes. However, this intriguing possibility requires more research before such speculations can be deemed valid (Alvergne & Lummaa, 2010).

Hypoactive Sexual Desire Disorder

Low or absent sexual desire is known as hypoactive sexual desire disorder (HSDD). The condition has only recently been characterized in men (Derogatis et al., 2012), but has been recognized for many years as being more prominent and prevalent among women (Brotto, 2010). The diagnostic category is somewhat controversial, especially in the context of premenopausal women, with claims that HSDD represents an unhelpful form of medicalizing what is often a socially induced and transitory situation (Jutel, 2010). Nevertheless, various medical approaches to the treatment of HSDD have emerged.

Whereas the problem for postmenopausal women lies with the cessation of ovarian sex steroid output, premenopausal women with HSDD in general do not appear to have low levels of sex steroids. For postmenopausal women, administration of estrogenic hormones (i.e., estrogen-replacement therapy) may be effective. However, estrogen-replacement therapy carries side effects and risks. Recent research has indicated that, for both postmenopausal and premenopausal women, androgen therapy can be effective in treating HSSD. This is because androgens such as testosterone bind avidly to androgen receptors within the brain and strongly influence sex drive. (The same process underlies male sex drive; however, it should be noted that androgen levels in men are typically around tenfold higher than in premenopausal women.) Thus, even in premenopausal women, androgen therapy is predicted to enhance sex drive and empirical findings support this notion (Chudakov , Ben Zion, & Belmaker, 2007). Typically, transdermal testosterone patches are employed to deliver a suitable level of androgenic stimulation to positively influence libido while avoiding masculinization. Early results indicate efficacy with minimal side effects, although the positive outcomes reported have not been unequivocal, and longer term studies of side effects are required before androgen therapy could become a mainstream treatment for HSDD (Davis & Braunstein, 2012; Kronawitter et al., 2009; Woodis McLendon, Muzyk, 2012). Even where HSDD may be due to psychological factors (e.g., depression, stress), androgen therapy may be effective (although the psychological causes should also receive direct attention).

Development of the Reproductive Tracts

Genetics of Sex Determination

In humans, male sexual development is initially driven by gene expression from the Y chromosome, with formation of the testes from generalized fetal tissues being the initial morphologically identifiable occurrence. The "default" developmental pathway is female; in other words, in the absence of a Y chromosome, the tissues that would otherwise have developed into the testis instead develop into the ovary. Testicular development is dependent upon the Y-linked testis-determining gene *SRY*; gonadal development in general (for both sexes) is also dependent on several other genes, both X-linked and autosomal. Beginning during fetal life, the testes secrete hormones, required for the development of the male reproductive tract, genitalia, and secondary sexual structures. The Y chromosome, in addition to harboring the *SRY* gene and thus serving as the "master switch" for the male development pathway, also contains genes essential for post-pubertal reproductive functioning; in particular, spermatogenesis. However, the Y chromosome contains relatively few functional genes. The X chromosome, by contrast, contains many more genes, of which only a minority are concerned with sexual development. In evolutionary terms, the Y chromosome is a relic of a distant ancestral autosome that has become 100% male-specific. In comparison, the X chromosome has evolved genes that are of advantage to both sexes. This distinction arises from the fact that, while the Y chromosome is exclusive to males, the X chromosome is possessed by both sexes. (See Schafer and Goodfellow [1996], Kucinskas and Just [2005], and Delbridge and Graves [2007] for useful reviews of the genetics of sexual differentiation.)

Hormonal Aspects

Male and female fetuses remain undifferentiated until the ninth week of development, with primordial ductal and sinal tissues providing the starting material for development of the genitalia and reproductive tracts. Within the *SRY*-induced male developmental pathway, androgenic sex steroids (primarily testosterone), secreted from the Leydig cells of the primordial testicular tissues, drive the development of male genitalia, the male reproductive tract, and masculine body characteristics. Under the influence of testosterone, one pair of ducts, the mesonephric, differentiates to become the key components of the male tract, including the vasa deferentia, ductus epididymides, and seminal vesicles. Testosterone is converted into dihydrotestosterone (DHT) in some target tissues: DHT drives the differentiation of the urogenital sinus to become the prostate and bulbourethral glands. Meanwhile, Sertoli cells, located within the primordial testicular tissue, secrete anti-Müllerian hormone (MSH); this hormone promotes the regression of another pair of ducts, the paramesonephric. In the absence of anti-Müllerian hormone, the paramesonephric ducts differentiate to become the top of the vagina, the uterus, and the oviducts. In the absence of DHT, the urogenital sinus differentiates to become the lower vagina and the Bartholin's and Skene's glands. In terms of development of the external genitalia, DHT drives the genital tubercle to differentiate into the penis; in the absence of DHT the same tissue develops into

the clitoris. (See Sajjad [2010] and Stukenborg, Colon, and Soder [2010] for useful reviews.)

Sex-Specific Brain Development

Development of a masculinized brain also occurs under the influence of sex steroids, with sex-specific "neuro-organizational" differences in sexual orientation and gender identity probably being established at this stage. However, because brain differentiation occurs much later *in utero* (i.e., during the first 2 months of pregnancy) than genital/physical differentiation (which occurs during the second half of pregnancy), the two developmental processes are largely independent of one another, and alterations in development (possibly mediated by hormonal signaling) could thus result in transsexuality or altered sexual orientation (Bao & Swaab, 2011; Savic , Garcia-Falgueras, & Swaab, 2010). Although the greatest effects on the brain occur during fetal life, puberty represents another neuro-organizational period, with the possibility that sex hormones may alter behavior. However, the possible role of pubertal hormones in respect to sexual orientation and gender identity is not yet fully understood, and further research in this area is encouraged (Berenbaum & Beltz, 2011).

Conclusion

This chapter has focused on contemporary issues and controversies in the science of human reproduction, with particular emphasis on aspects that affect sexual health and functioning such as sexual arousal, sperm transport, and sperm selection. It should be clear from the foregoing discussion that the science of human reproductive and sexual function comprises a wide range of disciplines, spanning molecular, cellular, physiological, and psychological fields. By the inherent intimate nature of the subject matter, the study of how humans procreate is associated with perhaps more contention than arises in most other scientific fields. Nevertheless, great progress has been made in recent years in terms of advancing our scientific understanding of the underpinning mechanisms and functions, with major implications for medical, nursing, and social practice. Moreover, technical advances such as high-resolution real-time imaging technology, coupled with exponentially increasing molecular genetic knowledge, look set to transform the study of human reproduction over the next several years. Such advances in research may provide data to address the unanswered questions of the scientific controversies associated with human reproduction and sexuality.

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