Hormonal Therapy for Male Sexual Dysfunction

Edited by Mario Maggi, MD, Director, Sexual Medicine & Andrology, Department of Clinical Physiopathology, University of Florence, Italy

Do you look after male patients suffering with sexual dysfunction?
Do you need to learn more about hormonal therapy as a treatment option?

Hormonal Therapy for Male Sexual Dysfunction offers a comprehensive rationale for hormonal therapy in male sexual disorders, and fully explains the language of sexual endocrinology and its application in clinical practice. It provides a clear understanding of how hormones work, which in turn will help you tailor more successful therapies for improved sexual response in your patients.

Edited by Mario Maggi, one of the world’s leading figures in sexual medicine, the tone throughout is practical, rather than academic. As a clinical ‘in the office’ or ‘at the bedside’ guide to effective patient care, it includes the following features:

• Key evidence, such as clinical trials, summarized in ‘Evidence at a Glance’ boxes
• Key references provided via the ‘selected bibliography’ at the end of each chapter
• Management algorithms and guidelines throughout
• ‘Tips and Tricks’ boxes – hints on improving outcomes via practical technique and patient questioning
• ‘Caution’ warning boxes – practical hints on how to avoid problems
• ‘Science Revisited’ – quick reminder of the basic science principles necessary for understanding

Hormonal Therapy for Male Sexual Dysfunction is essential reading for all those involved in the care of men with sexual dysfunction, including sexual medicine physicians, urologists, gynecologists and other healthcare providers in practice and in training.

Of related interest:
Interventional Techniques in Uro-oncology
Female Sexual Pain Disorders: Evaluation and Management

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Preface

The sexual lexicon is based on messages continuously exchanged among individuals, which can be rephrased and read under various perspectives. The capacity of exchange in sexual messages within the body is made possible largely by two different mechanisms: the nervous system, which transmits electrochemical signals as two-way traffic between brain and peripheral tissues or between tissues in reflex circuits; and the endocrine system, which releases chemical mediators termed hormones into the circulation for action away from their original sites. Hence, the endocrine system is an integral part of the sexual lexicon. However, only receptive individuals know the language and can read the message. Hormones are messages written in a biological language that can be easily read by receptive cells (those expressing the cognate receptor). Sexual hormones allow communication among lover's cells, because, even though hormones and receptors are physically distinct structures, they ultimately perform the same function.

Male sexual disorders often derive from a local or generalized misunderstanding of sexual messages. A better understanding of how hormones work and communicate will lead to the discovery of effective therapies to improve sexual communication. This book will provide the rationale for hormonal therapy in male sexual disorders, explaining the language of sexual endocrinology and helping to rephrase it when necessary.

Endocrinology has traditionally been defined as a branch of biological science that concerns itself with the actions of hormones and the organs in which the hormones are produced. Sexual hormones not only regulate gametogenesis, but also control the dimorphic anatomical, functional, and behavioral development of males and females that is essential for sexual functioning. It is of particular interest in this regard that no exclusive male or female sexual hormones have been identified. All hormones characterized to date are present in both sexes, and both sexes have receptor mechanisms that allow responses to all hormones. Sexual dimorphism is the result of differences in the amounts of individual hormones and differences in their patterns of secretion, rather than their presence or absence. It follows that sexual endocrinology requires a precise genetic programming that allows for the synthesis of an appropriate enzyme complement in the ovary or testis, which in turn catalyzes the formation of the appropriate amounts of hormones during the critical stages of life. The endocrinological control of sexual activity encompasses every phase of the process, including many behavioral aspects.

Sexual hormones might have multiple effects. An example of such a hormone is testosterone. Some of its diverse actions include fusion of the labioscrotal fold in the male embryo during embryogenesis, induction of male differentiation of the Wolffian ducts, regression of the embryonic breast (in some species), growth of the male urogenital tract, induction of spermatogenesis, growth of beard and body hair, promotion of muscle growth, retention of nitrogen, increased synthesis of erythropoietin, temporal regression of scalp hair, hyperplasia of the sebaceous gland with increased sebum production, development of prostatic
hyperplasia in aging males of several species, secretion of the ejaculate, and virilization of the male external genitalia (including penis), along with discrete hypothalamic nuclei. It was originally believed that androgens exerted these diverse effects by distinct mechanisms. However, one of the most important findings from genetic studies and from modern molecular biology is that diverge effects can be modulated by a single mechanism: the androgen receptor.

So, at the end of the day, sexual endocrinology is an important part of sexual medicine: read this book faithfully!

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Typical male gender development

Prenatal sexual differentiation

Sexual differentiation is a stepwise process starting with a difference of the sex chromosomes (XX for females, XY for males). The embryo starts off with two basic pairs of reproductive structures, the Müllerian ducts and the Wolffian ducts. A gene located on the Y chromosome (SRY) induces the development of the testis. A few weeks after conception, the testes will start to produce testosterone and Müller Inhibiting Substance (MIS). These hormones of the testes direct male development. The Wolffian ducts develop into male internal reproductive organs, and the MIS, produced by the Sertoli cells of the developing testes, causes the Müllerian ducts to regress. In the absence of a Y chromosome (and therefore testes and androgens), ovaries will develop. The Wolffian ducts will regress and the internal sex organs will develop along the female line, the default route. The external genitals also develop from identical structures. In males, testosterone and its derivative dihydrotestosterone (DHT) direct the genital tubercle to become the penis and the genital swellings fuse to form the scrotum, whereas in females, in the absence of testosterone, these structures become a clitoris and a labia.

Apart from the sexual differentiation of the genitalia, sex hormones in the prenatal environment influence the differentiation of the brain into male or female. Pre- and early neonatal exposure of the brain to sex hormones leads to permanent changes in the nervous system. These effects are referred to as organizational effects. From vertebrate models we learn that the steroid hormone testosterone accounts for the majority of the known sex differences in neural structure and behavior. In lower animals, the presence or absence of testosterone at the time of a critical period of brain sexual differentiation influences the morphology of certain brain nuclei. Like its influence on the development of the genitalia, the presence of testosterone leads to male sexual differentiation of the brain and results in male-typical behavior, while a
female brain and female-typical behavior are found to be the outcome of the absence of testosterone. When the testes are formed, they begin to produce testosterone and from this moment on there is a sex difference in testosterone concentrations between male and female fetuses. Through its effects on neurogenesis, cell migration, cell death, and the differentiation of neural circuits, testosterone has its effects on neuronal organization.

**Influence of prenatal hormones on male gender development in humans: evidence from non-clinical samples**

Gonadal hormones are also thought to influence the sexual differentiation of brain and behavior in humans, but the exact mechanisms and timing remain unclear. Early in life, sex differences are observed in play behavior and preferences. An approach to study the effects of prenatal testosterone on gender development is to relate hormonal levels in maternal serum or amniotic fluid to variations in subsequent gender-related (play) behavior in non-clinical samples. Maternal testosterone predicted the amount of male-typical behavior in daughters, as measured by parent questionnaires. Amniotic testosterone was found to be related to male-typical play behavior, as assessed by maternal reports of childhood sex-typed activities in male as well as female offspring. However, other studies did not find support for the hypothesized relationship between prenatal testosterone exposure and postnatal gender-related play behavior.

A frequently studied indirect measure of prenatal exposure to sex hormones is the ratio of the length of the second digit (2D, index finger) to the length of the fourth digit (4D, ring finger). The ratio is lower in men than in women and is assumed to be affected by exposure to prenatal androgens. Normal polymorphisms in the androgen receptor (AR) gene are reported to correlate with digit ratios in men. Using 2D:4D as a marker, prenatal androgen exposure has been found to be associated with behavior more commonly displayed by men than women and to be related to aggression, risk-taking, and disorders more common in men such as ADHD and autism.

Another research paradigm to study the influence of prenatal brain exposure to sex hormones comes from the study of opposite- vs, same-sex twin pairs. It is assumed that fetal androgens may be transferred from the male to the female fetus and that the female twin might thus be androgenized by her male co-twin. However, results of such studies have been found to be inconsistent.

**Early cognitive gender development**

From cognitive developmental studies we know that learning about being a boy or a girl starts in infancy. Babies as young as 9 months are already able to visually discriminate between the sexes. The ability to verbally label the sexes comes later, at around 28 months. As toddlers are often hardly aware of genital differences, they use hairstyle and clothing as a criterion for classification.

With regard to the concept of gender, children first learn to identify their own and others’ sex (*gender labeling*). Next, they learn that gender is stable over time (*gender stability*). Finally, they learn that superficial changes in appearance or activities (a boy does not become a girl overnight if he puts on a wig or plays with Barbie dolls) does not change one’s gender. This is the last stage of gender constancy (*gender consistency*). This last phase is reached between 5–7 years, but long before that age, children appear to have knowledge about gender stereotypes (for an overview see Ruble *et al.* 2006). For instance, 3-year-old children, who saw videotaped infants labeled male, rated these infants as “big,” “mad,” “fast,” “strong,” “loud,” “smart,” and “hard.” When labeled female, they were rated as “small,” “scared,” “slow,” “weak,” “quiet,” “dumb,” and “soft.” Three-year-olds also believe that “boys hit people.” Gender stereotype knowledge increases rapidly after 3 years of age and appears to develop throughout childhood. Once established,
gender stereotypes influence the way new information is processed. Children remember stereotype consistent information better than inconsistent information, and even distort inconsistent information. For instance, when a picture is shown to them of a woman flying an airplane, they may either report having seen a man flying the airplane or a woman doing something else, such as cooking.

According to some cognitively oriented theorists, children need only basic information rather than extensive knowledge about gender to further develop gender role behavior. For instance, children prefer same-sex toys, imitate same-sex models, and reward peers for gender-appropriate behavior before they reach complete gender constancy. Therefore, a complete understanding of gender is perhaps not important in the very early stages of gender development.

Gender development is a process that not only involves cognitive aspects but also involves affective meanings. As soon as a child identifies with one of the sexes, these values will affect their self-perception and self-concept. For instance, boys are usually proud of being a boy and look somewhat down on girls.

Gender segregation
At very early ages children become interested in same-sex playmates. Boys like other boys better than girls and spend a fair amount of time in the company of other boys. Changing this peer preference appears to be difficult.

Children thus spend an important part of their time in all-male or all-female groups. Boys tend to play in larger groups, play in more public places and with less proximity to adults, and play rougher and with more body contact. Boys fight more and their social interaction is oriented more toward issues of dominance. Girls' groups are less hierarchically organized and their friendships are more intense. Girls appear to use language to create and maintain relationships, to criticize others in acceptable ways, and to interpret accurately the speech of other girls. In boys, speech is used to attract and maintain an audience, to assert one's position of dominance, and to assert oneself when others have the floor. So gender segregation has far-reaching consequences for children's social development and friendships.

The influence of the environment on gender development
Children also learn about gender by observation of role models and by differential treatment. This differential treatment may be more or less direct (e.g. playing different games with boys than with girls) or be more subtle or indirect (e.g. blue and pink clothing). An immense body of literature supports the notion that parents, other adults, teachers, peers, and the media are gender-socializing agents. For instance, mothers talk more to daughters than to sons, teachers praise and criticize boys more than girls, and peers reinforce same-sex and punish cross-sex behavior. In experiments in which the actual sex of an infant is unknown, adults even interact differently with children labeled as boys than with children labeled as girls.

Adults and children are not just influencing gender development by their reinforcement of behaviors. As role models, parents and peers also shape children's gender attitudes and behaviors. Furthermore, gender development seems to be strongly influenced by the media. This was nicely illustrated by an older study among children living in a Canadian town unable to receive television. Before television was introduced, they were less traditional than a control group. Two years later their attitudes had changed dramatically in the more traditional direction.

Besides biological factors, such as prenatal exposure to testosterone, environmental and psychological factors also play a role in male gender development.