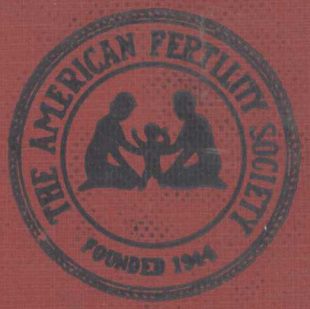
MODERN TRENDS in Infertility and Conception Control



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Modern Trends in Infertility and Conception Control

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Preface

Since its establishment in 1944, The American Fertility Society (originally known as The American Society for The Study of Sterility) has dedicated itself to education, service, and scientific advances in reproductive biology and infertility. From its inception, the Society has conducted annual national meetings, and in 1950 the Society published the first volume of its official journal, *Fertility & Sterility*. This journal has grown to assume a position of international distinction among scientific journals devoted to reproduction. The programs of the Society's annual meetings and the content of *Fertility & Sterility* reflect the diversified composition of The American Fertility Society: clinicians and basic scientists; gynecologists, urologists, pediatricians, and endocrinologists; family practitioners and demographers; medical practitioners and veterinarians. The unique bond that ties such heterogeneous scientific groups is an underlying dedication toward understanding reproductive processes for the purpose of enhancing fertility.

Since its initial publication in 1950, *Fertility & Sterility* has contained a large number of classic papers. A prime example is that often-quoted article by Noyes, Hertig, and Rock entitled "Dating the Endometrial Biopsy." Almost as if it represented a vote of confidence, this classic was the first article to appear in the Journal (Volume 1, page 3, 1950). Many other articles that have appeared over the years are of similar stature and importance. In 1975, the section entitled *Modern Trends in Infertility and Conception Control* was established. The primary objective of this new section has been to provide the practicing physician with the most current developments in diagnosis and management of reproductive problems. The *Modern Trends* section has served as a reflection of the current state of the art in infertility, reproductive endocrinology, and conception control. Each article appearing in *Modern Trends* has been carefully planned and selected. Its authors are among the most authoritative in their fields. In each case the subject matter is delivered in a clear, concise, and critical manner. The material is current and has been of well-recognized significance and usefulness to the reader.

The success of the *Modern Trends* section of *Fertility & Sterility* led to compilation of the first 36 articles into a single volume, *Modern Trends in Infertility and Conception Control,* published in 1979. That textbook, widely circulated and read throughout the world, has served as a ready reference for those practicing reproductive medicine, as well as for teachers and students. Advances in reproductive biology and progress in the care of the infertile have occurred at a dramatic pace. Procedures have been developed and applied to diagnosis and management over recent years that may not even have been

considered plausible a decade ago. Because of the progress in this field, an up-to-date, clinically oriented yet physiologically based textbook is essential to current practice. *Modern Trends in Infertility and Conception Control,* Volume 2, is entirely new. Each of the 36 contributions has served as a lead article in *Fertility & Sterility* over the past three years. Volume 2 covers material not included in Volume 1 and should serve as an ideal companion piece to its predecessor. The chapters fall smoothly in place within eight sections.

1. Reproductive Endocrinology
2. Pharmacologic Agents in Infertility Therapy
3. Diagnostic Procedures in Infertility
4. Surgical Procedures for Correcting Infertility in the Female
5. Pregnancy and Pregnancy Outcome in Infertile Couples
6. Male Infertility
7. Contraception and Sterilization
8. Psychological Aspects of Infertility

Each section is preceded by an introduction synthesizing the theme of the chapters included within that specific section. The book has been painstakingly indexed to enable rapid reference to specific subject matter. The format and design were enhanced by Lippincott-Harper & Row, Publishers. The editors were ably assisted in preparation by Mrs. Kathleen Bracken, Mrs. Carol Olson, and Mrs. Margaret Rose.

The material contained in this book will complement the first volume of *Modern Trends in Infertility and Conception Control.* Both volumes should serve as fundamental textbooks for the basic infertility/reproductive endocrinology library. I anticipate that the rate of accumulation of new knowledge and experience in the field of reproduction will continue to flourish, meriting publication of the third volume of *Modern Trends* three years hence.

Edward E. Wallach, M.D.

Foreword

The ability to reproduce and to perpetuate the species is one of the most remarkable features of a living system. At the molecular level, reproduction is a function of the unique capacity of the nucleic acids for self-replication. At the full organism level, reproduction ranges from the simple fission of bacteria to the complex functional, structural, and behavioral processes of higher animals. In such higher animals as humans, reproduction involves not only genetic transfer of biological information to the ensuing generation but also the endocrine regulation of the development of the genital tracts, oogenesis, ovulation, and spermatogenesis. Involved too are regulatory means to ensure that eggs and sperm are released synchronously so that they meet at the appropriate place and form a fertilized egg and zygote and ultimately become implanted. This process is cyclic, and one can study reproduction by beginning at any point in that cycle.[1]

This textbook is intended to provide an update of contemporary basic and clinical investigations conducted at many points in the reproductive cycle, placing emphasis on the relationships of clinical endocrinology to physiology, genetics, biochemistry, and immunology. The book is directed to serious students of reproductive medicine and is clinically oriented because it is intended primarily for the use of those directly concerned with patient care. In every sense this textbook has been a collaborative effort of many distinguished scientists, teachers, and clinicians. The result is a current, comprehensive, and integrated source of ready information on a wide range of topics in infertility and conception control.

Roger D. Kempers, M.D.

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SECTION ONE

Reproductive Endocrinology

The strides made in reproductive endocrinology during the past decade may be attributed partly to enhanced awareness of the interrelationships among the hypothalamus, anterior lobe of the pituitary gland, and ovaries. Although the pituitary gland and hypothalamus have long been recognized as closely related anatomically and physiologically, only relatively recently has enough evidence been accumulated to establish neurohormones as the link between the two structures. Further, biochemical events within the brain involving synthesis of biogenic amines, including norepinephrine, serotonin, and dopamine, appear to regulate hypothalamic function. The stimulatory and inhibitory effects of the biogenic amines may serve as the link between the environment (internal and external) and hypothalamic control over pituitary function.

A second factor responsible for expanding our appreciation of reproductive endocrinology relates to the ability of radioimmunoassay to detect rather small concentrations of steroid and peptide hormones in blood and urine. The chapters in this section attest to an advanced state of sophistication that has been achieved in reproductive endocrinology. They also emphasize the importance of sensitive, accurate, and practical endocrine assays and central nervous system regulation of reproductive endocrinology. This section contains material on hypothalamic-pituitary disturbances in reproduction, prolactin excess, pathophysiology and clinical aspects of corpus luteum function, and management of problems associated with androgen excess.

Characteristic of prolactin-secreting pituitary tumors are galactorrhea and amenorrhea. The observations that both of these clinical symptoms may be found in normal persons and that pituitary adenomata may exist without hyperprolactinemia compound the problems inherent in diagnosis of pituitary adenomata. The advent of reliable assays of prolactin in blood, supplemented by rapid advances in neuroradiology, has brought to light a condition that until recently was frequently overlooked in the gynecologic patient who had ovulatory failure in association with microscopic pituitary lesions. That a drug that effectively suppresses prolactin secretion has become available for clinical use serves to emphasize our need to diagnose this condition in its early stages. Newer neurosurgical techniques that allow microsurgical resection of pituitary adenomata by means of a transsphenoidal approach offer additional approaches to management. Pepperell raises seven basic questions about prolactin in the infertile couple and updates the complexities associated with the problem of hyperprolactinemia. Questions include [1] which patients should have serum prolactin levels measured; [2] what studies are indicated in patients with hyperprolactinemia; [3] how can ovulation be induced in hyperprolactinemic patients; [4] what is needed for the patient who fails to respond

to bromocryptine; [5] can the hyperprolactinemic patient who establishes a pregnancy anticipate additional problems; [6] should bromocryptine be used for conditions other than hyperprolactinemia; and [7] how should we manage the patient with hyperprolactinemia who is not interested in establishing a pregnancy. The reader is urged to refer to Kinch's chapter in the next section for futher review of the pharmacology and use of bromocryptine in infertility. Pepperell, however, has focused on the major questions needing resolution. That pituitary adenomata have existed for longer than prolactin assays, polytomography, CAT scans, and bromocryptine serves to emphasize that we are still scratching the surface in the management of patients with hyperprolactinemia. Reported experiences from centers around the world will ultimately help to develop acceptable and efficacious management protocols. We still need to know whether bromocryptine can be applied therapeutically to reduce the size or to retard the growth of known pituitary adenomata. The availability of sensitive neuroradiologic techniques provides a sensible mechanism to follow the efficacy of bromocryptine in reducing tumor size.

Luteal phase dysfunction continues to be a controversial issue. Probably a handful of physicians today doubt the existence of such an entity or, at best, feel that luteal phase defects are overdiagnosed. Ever since the description by Jones, we have been told that defects in the luteal phase account for 35% of repeated first-trimester pregnancy losses and 3.5% of infertility problems.[1] The traditional criteria for diagnosis depend on a lag in endometrial maturation of 2 or more days behind what would be anticipated from the presumed day of ovulation and the onset of subsequent menses. Simply stated, luteal phase defects represent conditions in which progesterone is produced in insufficient quantities or for too short an interval after ovulation. The classic studies by Strott and colleagues and Sherman and Korenman have pointed to the possible genesis of specific types of luteal phase defects from inappropriate follicular development in the preovulatory phase of the cycle.[2–4] Insufficient pituitary gonadotropin stimulation early in the cycle leads to improper development of the dominant follicle, with deficiencies in estrogen secretion in the preovulatory phase and inadequate progesterone secretion after ovulation. The model for studying luteal dysfunction established by diZerega and Hodgen clearly associates luteal dysfunction with aberrant folliculogenesis and a cascade of deficiencies in the preovulatory follicle and corpus luteum. This enlightening information emphasizes the need for diagnostic technology and treatment to be applied to the preovulatory phase of the cycle as well as after ovulation. The various factors potentially responsible for luteal phase defects, including hyperprolactinemia, are reviewed by Andrews. His chapter explores the pitfalls of different pharmacologic approaches to correction of the problem, including substitutional treatment with progesterone, gonadotropin, clomiphene-induced ovulation, and bromocryptine. Concerns about teratogenicity associated with the use of pure progesterone are carefully analyzed by Andrews and largely dispelled. Progesterone and 17-hydroxyprogesterone are naturally occurring steroids to which the oocyte and fetus are normally exposed in great quantity. These two steroids should not be confused with synthetic progestogens that have been implicated in the development of congenital anomalies in babies born to mothers exposed to these synthetic preparations.

Androgen excess represents a cosmetic problem to the affected person as well as a frequent medical problem. The degree of the medical problem may extend from anovulation and consequent infertility to life-threatening conditions such as adrenal or ovarian neoplasms. Intermediate may be adrenal enzymatic defects leading to adrenal hyperplasia. Three chapters approach this problem from divergent aspects. Maroulis looks at androgen excess and reproduction, providing definitions and a framework for studying the patient

with androgen excess. His approaches involve selection of appropriate endocrine assays and dynamic tests. The material provides standards for interpreting dynamic tests and approaches to management of the hirsute female.

Very few reproductive endocrinologists are not cognizant of the classic paper by Goldzieher and Green.[5] This widely read and often-quoted paper reviewed the world's literature on polycystic ovaries and provided insight into variations in clinical manifestations of the disorder. It has taken virtually 20 years for Goldzieher to update his concepts on polycystic ovarian disease, but in so doing he calls upon the intervening expanded pool of knowledge of neuroendocrinology and individual gonadotropin fluctuations responsible for ovulation. From the patient's history through symptomatology, pathophysiology, laboratory findings, and management, Goldzieher supplants his original classic of 1962 with an authoritative 1982 compendium on a widely diagnosed and frequently enigmatic condition.

The similarity between manifestations of adrenal and ovarian disorders has been apparent for many years. Bongiovanni, an authority and pioneer in describing and classifying adrenal hyperplasia, describes an entity at one time considered controversial and simultaneously closes the gap between adrenal and ovarian disorders. Whereas adrenal hyperplasia had for many years been considered a congenital disorder based on a deficit in specific enzymatic systems responsible for steroid biosynthesis, Bongiovanni points out that acquired adrenal hyperplasia is a real entity. Late-onset 21-hydroxylase deficiency is well established, occurring in older women who may experience virilization at the time of puberty or beyond. The fact that 3β-hydroxysteroid dehydrogenase deficiency occurs in adults and may occur in both gonadal and adrenal tissue simultaneously raises exciting possibilities about the pathogenesis of various ovulatory disturbances, the pathophysiology of hirsutism, and indeed the appropriate form of management of such problems.

The syndrome of anorexia nervosa is characterized by behavioral disturbances accompanied by marked weight loss and amenorrhea. This entity is being seen or diagnosed with increasing frequency. The rising incidence may stem from more widespread emotional disturbances, from a more diet-conscious society, or from current emphasis on physical exercise. Recently, endocrine assays have given a reasonably clear picture of changes in gonadotropin (LH and FSH) levels, patterns, and oscillations during childhood and puberty. The fact that patients with anorexia nervosa revert to prepubertal hormonal patterns and that refeeding recapitulates the progressive changes seen in puberty points to anorexia nervosa as a hypothalamic problem instead of, or in addition to, a psychologic disturbance. Long recognized is that malnutrition influences fertility, but recently recognized is the link between starvation states and anorexia nervosa, a link that raises significant possibilities for future management. Eisenberg's chapter brings this problem up-to-date and raises some distinct questions for the future.

—Edward E. Wallach, M.D.

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