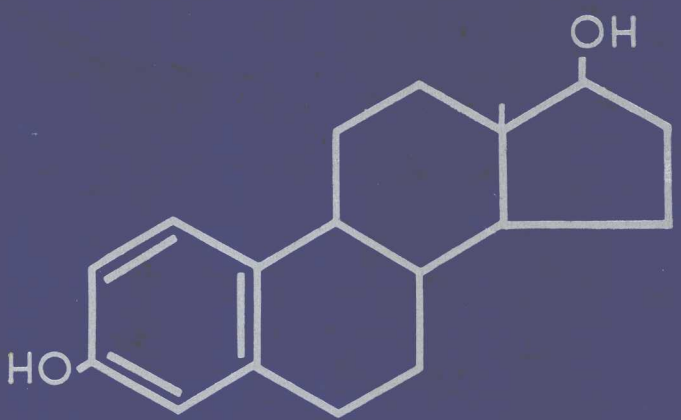
ENDOCRINOLOGY OF PREGNANCY

James R. Givens, editor



ENDOCRINOLOGY OF PREGNANCY

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Volume 1
GYNECOLOGIC ENDOCRINOLOGY (1977)

Volume 2
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DISORDERS (1978)

Volume 3
THE INFERTILE FEMALE (1979)

Volume 4
CLINICAL USE OF SEX STEROIDS (1980)

Dedication

Dr. Arnold Klopper is Professor of Reproductive Endocrinology, Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen, Scotland. He received his B.Sc. degree with a major in physiology from Witwatersrand in 1943 and graduated from medical school at Witwatersrand in 1946 with the degree of M.B. and Ch.B. He completed his house surgeonships in Johannesburg in 1950 and then served as a Junior Registrar in Obstetrics and Gynaecology at the British Hospital for Mothers and Babies, Woolwich. After completing his postgraduate work at Hammersmith he qualified for the MRCOG in London in 1952. In 1955 Dr. Klopper obtained a Ph.D. in biochemistry at the University of Edinburgh and joined the scientific staff of the Medical Research Council in Obstetric Medicine Research in Aberdeen. He advanced through the academic ranks at Aberdeen to his present post of Professor of Reproductive Endocrinology.

Dr. Klopper has made extensive research contributions in the area of reproductive endocrinology. He has been the coeditor of four books and a coauthor of numerous others and has written more than 250 scientific papers dealing with various aspects of endocrinology. Dr. Klopper is not only a distinguished scientist of international renown but also a warm, personable human being who projects a compassionate, caring attitude, and has a keen sense of humor.

This volume is dedicated to Dr. Klopper, Distinguished Keynote Speaker at the Fifth Annual Reproductive Medicine Symposium.

JAMES R. GIVENS, M.D.

Preface

ENDOCRINOLOGY OF PREGNANCY was the title of the Fifth Annual Reproductive Medicine Symposium sponsored by the Department of Obstetrics and Gynecology of the University of Tennessee College of Medicine. This volume contains the proceedings of that symposium, which was held between March 3 and March 5, 1980, in Memphis. The speakers submitted prepared manuscripts of their presentations for publication. The panel discussions are edited transcriptions.

Like the symposium itself, the book is divided into two parts, dealing with normal and abnormal pregnancy topics. The maternal endocrine changes of normal pregnancy are discussed first, including the endocrinology of early pregnancy, changes in the maternal pituitary-adrenal axis, and the pituitary-thyroid axis. Also included in this subsection are the alterations in carbohydrate, fat, protein and mineral metabolism. The fetal aspects of normal pregnancy are discussed next, including adrenal steroidogenesis, fetal growth and development, and the initiation of labor. The subsection devoted to the endocrinology of the placenta deals with the structure-function relationships, peptide hormone synthesis, and the newly discovered placental peptides and their role in pregnancy.

In the maternal section of abnormal pregnancy the topics discussed are recurrent abortion, diabetes mellitus, hypertension, as well as thyroid, adrenal, and gonadal disorders. The fetal and placental subsection covers abnormal sexual differentiation, premature labor, diagnostic amniocentesis and the hormonal assessment of the fetoplacental unit.

The continued cooperation and support of Preston V. Dilts, Jr., M.D., Chairman of the Department of Obstetrics and Gynecology of the University of Tennessee College of Medicine, and of the staff of the Division of Continuing Education is gratefully acknowledged. The skillful assistance of Gabriela Radulescu and of the staff at Year Book Medical Publishers was essential to the publication of this volume. The expert secretarial assistance of Carolyn Minga and Jeanette Austin is also gratefully appreciated.

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Endocrinology of Early Pregnancy

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Introduction

PREGNANCY BEGINS AT DIFFERENT TIMES: for the fetus it begins at fertilization, with formation of the zygote, which immediately enters the process of embryonic development; for the mother, it begins some time later, with recognition of the presence of the blastocyst through an endocrinologic signal. Previously cyclic ovarian function is replaced by pregnancy-specific endocrine mechanisms initiated by the elaboration and secretion of human chorionic gonadotropin (hCG), which may be produced by the developing zygote, preimplantational blastocyst, or syncytiotrophoblast of the early implantation site. The purpose of this review is to describe the endocrinology of early pregnancy; however, a complex interplay of biochemical and physiologic processes precedes implantation and the initiation of fetal development. Since these interactions are crucial to the development of a normal endocrinologic milieu in early pregnancy, a brief description is appropriate.

Maternal and Fetal Preimplantational Events

MATERNAL PREIMPLANTATIONAL EVENTS

Preovulatory Determinants of Luteal Function

Certain aspects of follicular development clearly predetermine the adequacy of the function of the corpus luteum. The factor initiating

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follicular development is unknown, but an adequate pool of follicles is essential, and development of the follicle ovulated in any cycle probably begins several cycles before. The dominant follicle is chosen early in the cycle, certainly by six to seven days prior to ovulation.[1] The increase in FSH that precedes menstruation in the preceding cycle may be necessary to the synchronization of follicular development. FSH is an important hormone with many functions integral to adequate follicular development.[2-5] These include: (1) synthesis of receptor sites for FSH on the granulosa cells (GCs); (2) synthesis of receptor sites for LH on GCs; (3) induction of GC hyperplasia; (4) induction of aromatase enzyme activity in the GCs; (5) formation of the antrum; (6) stimulation of mucopolysaccharide synthesis within the follicular fluid; (7) stimulation of cumulus expansion by inducing synthesis of hyaluronic acid; and (8) stimulation of plasminogen activator production by the GCs. Overall, the major function of FSH is to induce and further mechanisms by which granulosa cells develop increased sensitivity to gonadotropin stimulation. The resultant synthesis of estradiol is a cooperative effort between theca and granulosa cells, and results in a milieu appropriate for ovulation. Estradiol functions via intraovarian mechanisms to increase blood flow and receptor synthesis, "sensitizes" the cells to gonadotropin stimulation, and synergizes with FSH and then LH in follicular selection and development.[6] The increasing estradiol output initiates the LH surge by a positive feedback at the pituitary level. The flood of LH results in two events, ovulation and luteinization. The physical act of ovulation probably occurs via a mechanism that involves prostaglandin $F_2\alpha$ action; plasminogen activator induced by LH itself, or by the accompanying FSH increase, may also play a role. The maturing oocyte surrounded by cumulus cells is expelled from the graafian follicle and enters the fallopian tube where further maturation occurs prior to fertilization (Fig 1), which is at least partially determined by the hormonal milieu of the tubal fluid. The FSH-induced synthesis of receptors for LH on the granulosa cells prepares them to be responsive to the LH stimulus; luteinization involves morphological and biochemical changes and the subsequent progesterone-dominated steroidogenesis. Multiple activities must be coordinated prior to ovulation to permit adequate luteinization of the corpus luteum and production of sufficient progesterone to promote implantation and support of an early pregnancy.

The final determinant of adequate luteal activity is the continued stimulation of granulosa cell progesterone synthesis by low levels of LH. However, with time these cells become less sensitive to LH stimulation. This process of receptor inhibition, called down-regulation,

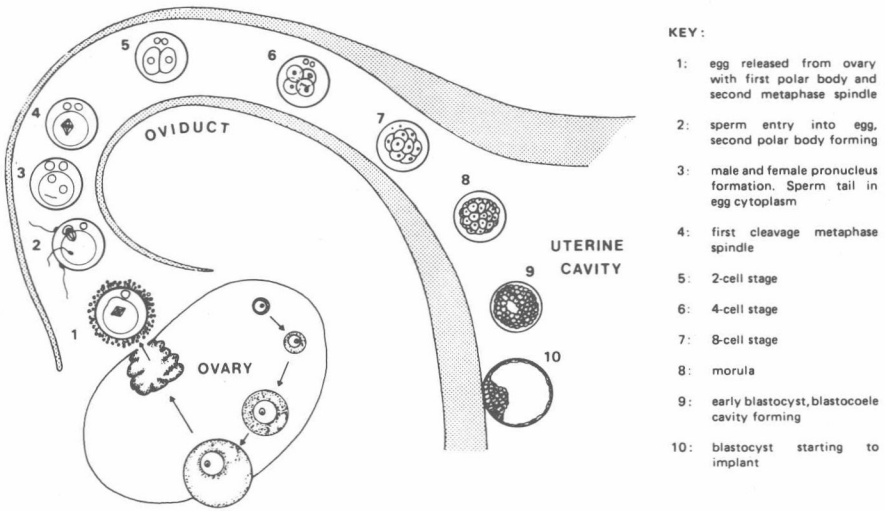

Fig 1.—Diagrammatic representation of follicular growth, ovulation, fertilization, and preimplantation. (Reprinted with permission from Whittingham, D.G.: "In-Vitro Fertilization, Embryo Transfer and Storage." *Br. Med. Bull.* 35:105–111, 1979.)

may be mediated by estradiol; the decreased cellular sensitivity to the LH stimulus produces a mechanism for the control of the duration of luteal function[7] and causes ultimate regression of the corpus luteum. Cellular and hormonal cooperativity is essential for adequate luteal function.

Endometrial Development

Although the myometrium, breast and fallopian tube undergo changes induced by the sex steroids, the major target organ of follicular estradiol and luteal progesterone output is the endometrium. Endometrial repair begins by the second or third day of menstrual desquamation with growth of endometrial cells from the bases of the remaining glands.[8] Throughout the 12 to 14 days of the normal follicular phase, estrogen acts on both stroma and glands as a growth-stimulating hormone, producing a proliferative pattern. After ovulation and luteinization of the granulosa cells, circulating progesterone induces a continuum of predictable change in the endometrium; biopsy of the tissue and histologic interpretation can serve as a bioassay of progesterone output. The earliest progesterone-induced secretory change is a rapid increase in RNA synthesis and the formation of glycogen-filled subnuclear vacuoles in the glandular epithelium.

The surface architecture of the endometrium continually changes under the progesterone stimulation, with modification of the microvilli necessary to ensure contact between blastocyst and endometrial lining, and the induction of an electrochemical charge to further this attraction. Enzyme induction also occurs. All of this results by day 22 in an endometrial site receptive for implantation.[9] Clinical studies suggest that if endometrial development is inadequate because of a decrease in progesterone output, either implantation will not occur or a first-trimester abortion may result. A defect in progesterone output, a so-called inadequate luteal phase, can be responsible for infertility and occult and early spontaneous miscarriage. Progesterone secretion is important to produce a properly prepared endometrial implantation site.

Fetal Preimplantational Events

Oocyte Maturation

The primordial germ cells that migrate from the wall of the yolk sac to the germinal ridge undergo a period of intense mitotic activity before entering meiosis; these primary oocytes then remain in the diplotene stage of meiosis I until maturational divisional processes are resumed 36–48 hours prior to ovulation.[10] Follicular growth to the graafian follicle stage is completed before the oocyte resumes maturation, which is probably initiated by the LH surge. The oocyte grows during primary follicle development and has a high rate of endogenous RNA synthetic activity. This occurs during the early stages of follicular development, but is complete before the formation of a secondary follicle, when the antrum develops, and by the time the surrounding granulosa cell layer has been thickened.

Growing follicles synthesize, secrete, and metabolize several types of compounds, including polypeptides and steroid hormones. Some act as inhibitors within the follicle or ovary, whereas others influence the central nervous system. Steroids are probably involved both in the late stages of nuclear maturation, as documented by McGaughey,[11] and in regulation of cytoplasmic maturation, as shown by a number of experiments summarized by Thibault.[12]

The nonsteroidal intrafollicular regulators have been reviewed and described by Channing.[13] The granulosa cells appear to be the source of oocyte maturation inhibitor (OMI),[14] the intrafollicular substance which suppresses meiosis and arrests the oocyte in the dictyate stage of meiosis I (Fig 2). Its action is overcome when follicles are exposed

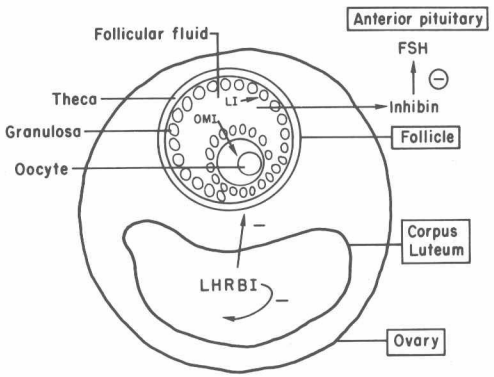

Fig 2.—Diagrammatic representation of the intraovarian inhibitors: oocyte maturation inhibitor (OMI); luteinization inhibitor (LI), luteinizing hormone receptor binding inhibitor (LHRBI), and inhibin or folliculostatin (LH-RBI). (Reprinted with permission from Channing, C.P., et al: "Studies on an Oocyte Maturation Inhibitor Present in Porcine Follicular Fluid" in, *Novel Aspects of Reproductive Physiology,* Spilman, C.H., and Wilks, J.W. (eds.): Spectrum Press, NY, 1978, pp. 37–54.)

to LH, if they become atretic, or when oocytes are removed from follicles and cultured in suitable fluid even in the total absence of gonadotropin hormones. OMI is present in the fluid of porcine antral follicles. It is a small polypeptide with a molecular weight (mol wt) on the order of 2,000. Cumulus cells appear to be required for the inhibitory action of OMI, since no inhibition of oocyte maturation is seen when follicular fluid containing OMI is added to culture medium containing oocytes denuded of cumulus cells.

Luteinizing-hormone receptor binding inhibitor (LH-RBI) reduces the binding of LH to luteal cells, blocks LH-stimulated progesterone biosynthesis, and is a small polypeptide.[15] Growing follicles may secrete less and less of it until finally they can be stimulated by LH. A third substance, luteinization inhibitor (LI), suppresses both the morphological and steroidogenic luteinization of granulosa cells in monolayer cultures, and is found in the antral fluid of small follicles; it is unlikely to have its source in the oocyte, and its mode of action may depend on phosphodiesterase to reduce levels of cyclic AMP, for it does not influence the binding of LH to granulosa cells. A fourth inhibitor, inhibin or folliculostatin, is produced by graafian follicles and may act centrally to regulate the secretion of FSH. It is found in large amounts in small follicles, is trypsin-sensitive and nonsteroidal, and has a molecular weight of 10,000. Fluctuating levels of folliculostatin may be responsible for the changing secretion of FSH during the

menstrual cycle, at menopause, and in conditions involving the disordered growth of follicles.

Resting oocytes in the diplotene stage have a prominent nuclear membrane called the germinal vesicle. Disintegration of the germinal vesicle, followed several hours later by nuclear breakdown, is the first step of meiotic maturation; this is followed by chromosome condensation and alignment on the metaphase I spindle, separation of homologous chromosomes and emission of the first polar body, and arrest of nuclear progression at metaphase II. Several possible mechanisms appear to control this event, as reviewed by Schuetz.[16] In some species, fertilizing sperm trigger the resumption of meiosis; in amphibians, progesterone is a primary stimulator. Peptide maturation-promoting factors, possibly secondarily induced by steroids, are postulated to be the initiating mechanism in other situations. In the human, regulation of the onset of oocyte nuclear maturation involves the interaction of an initiating signal for meiotic development, which may be the LH surge, and oocyte meiosis inhibitor, probably produced by the granulosa cells of differentiating ovarian follicles. The resumption of meiosis therefore is mediated by a hormonal stimulus in vivo, and the initiating influence is probably the LH surge. LH greatly stimulates the production of progesterone and androstenedione; oocyte maturation is always associated with increased levels of steroids in the follicular fluid. So in mammalian oocytes steroids may have some role in facilitating the resumption of meiosis.

It is only after nuclear progression to metaphase II that oocytes are competent to be fertilized. During this period, not only meiotic events occur, but also an extensive reprogramming of oocyte metabolism, including qualitative changes in the nature of the protein synthesized, quantitative changes in the rate of synthesis, extensive alterations in the ultrastructure of various organelles and inclusion bodies, and oocyte enlargement. Oocyte maturation refers to the entire sequence of nuclear, cytoplasmic and membrane changes, beginning with resumption of meiosis and ending in a rest period at the second meiotic metaphase.

Ovulation and Fertilization

LH- and FSH-dependent morphological and biochemical changes result in the physical release of the now detached oocyte and its surrounding cumulus cells from the follicle, and in the luteinization of granulosa cells. Once ovulated, the oocyte enters the fallopian tube, where fertilization occurs in the ampulla. This requires a complex