Progress in Conception Control 1968

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FOURTH PHYSICIANS' CONFERENCE

A Report of a scientific discussion held in Chicago at the time of the Sixteenth Annual Meeting of the American College of Obstetricians and Gynecologists, May 1968

Edited and with an Introduction by

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Contents

CHAPTER		PAGE
Introduction		9
	DEAN L. MOYER, MD	
1.	*Effects of Synthetic Steroids on Serum Gonadotropins: Determination by Radioimmunoassay*	13
	ROBERT B. JAFFE, MD A. REES MIDGLEY, JR., MD	
2.	*Thromboembolic Phenomena in Relation to Oral Contraception*	25
	DAVID CHARLES, MB	
3.	*Coagulation and Fibrinolysis: Normal Pregnancy and Menstrual Cycle, Sequential Anti-ovulatory Regimen*	44
	JACQUES LORRAIN, MD	
4.	*Use, Effectiveness, Continuation Rates of Oral Contraception Buffalo Planned Parenthood Center 1962 to 1967*	56
	JACK LIPPES, MD	
5.	*The Long-Term Use of a Sequential Regimen*	66
	C. CURTIS YOUNG, JR., MD	
6.	*The Missed Pill: Preliminary Report*	78
	J. L. JACKSON, III, MD	
7.	*Management of the Minor Side Effects of Oral Contraceptives*	87
	RICHARD P. DICKEY, MD CLYDE H. DORR, II, MD	

8. *Psychophysiologic Aspects of Oral Contraception* 95
WILLIAM S. KROGER, MD

9. *Carbohydrate Metabolism and the Contraceptive Steroids* 101
SAMUEL S. C. YEN, MD

10. *Plasma Cortisol in Relation to Menstrual Cycle and During Oracon Therapy* 109
H. OLIVER WILLIAMSON, MD

11. *Birth Control in Reverse* 119
ROBERT B. GREENBLATT, MD

Conclusions 133
DEAN L. MOYER, MD

Index 137

Introduction

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Gentlemen, the need for mankind to increase control over his environment is becoming even more apparent. The necessity for such control is greatest in the realm of the reproductive processes. During the past several decades, significant advances have been made in the control of mortality, and, as a consequence, world population has increased at an unprecedented rate. Even though modern medicine has significantly lengthened the average life span, death control has been most dramatic in newborn and infant populations. With a relatively rapid increase in national or world populations, the level of the standard of living will be directly affected. In many societies, the motivation for the improvement of living standards is the intelligent control of the family size. Lower income groups in particular have a higher parity, and with an increasing number of children more and more of their limited income is directed toward the basic necessities of rearing the children. Thus today one of man's most pressing problems is the development of medical technology that will provide a choice of effective and safe birth control methods.

Scientists from different parts of the world are making an intensive effort to solve the problems of birth control. In general, there are three methods by which birth rates may be reduced in any society: abortion, sterilization, and contraception. Although the first two methods have found acceptance in some countries and have been temporarily effective, their long-term value appears to be the least significant of the three methods. Methodology showing more promise is the development of acceptable contraceptive measures. Research into the fundamental physiologic activities of reproduction and the application of these phenomena to human patients has been progressing at an increasing pace during the past twenty years. Prior to that time, motivation for research into the reproductive processes was usually the desire to find therapeutic weapons to cure infertility rather than to prevent fertility. Although relatively crude attempts at contraception by our standards have been made for centuries, it was not until the imaginative development of the ovulation inhibitor pill by Pincus and Chang, and the introduction to human patients by Pincus, Rock and Garcia, that attempts to control birth began to flourish scientifically.

There are no indications that research will stop at this point, and, in fact, second-generation contraceptive preparations are already available to potential users. Of these methods, studies have shown that Oracon is an effective birth-control medication that tends to simulate the normal hormonal patterns and at the same time to protect the woman against an unwanted pregnancy. To develop contraceptive knowledge and techniques and to make them readily available to large groups of women require a great multidisciplinary effort. Basic scientists, physicians and many paramedical professions are needed to accomplish this job. Physicians are involved not only in the discovery of new knowledge and methodology but in the dissemination of the knowledge. In addition, it is the physician's responsibility to make a medical judgment in prescribing a medicinal compound to his patient by evaluating the known benefits of the preparation and comparing these to any potential risk that may involve his patient.

The development of an ideal contraceptive method requires

the consideration of several goals. The first requirement is that a contraceptive method must have a high rate of effectiveness in preventing pregnancy. The contraceptive method should be presented in a form readily acceptable to the user, so that its continued use may be ensured. In addition, when any method is utilized that electively prevents pregnancy, both the short- and long-term side effects should be minimized in severity. In the event of a small number of failures of a method to control birth, the offspring should not show a greater number of congenital anomalies than normally expected in the population.

Reversibility of the contraceptive method is essential, so that married couples who decide to continue their family may do so within a reasonable amount of time. Many individual and national differences occur in attitudes toward fertility control, and consequently a variety of methods should be available to the family unit so that at least one of these methods may meet their needs. For example, many women would prefer to know that they may control their fertility by taking a daily medication, while others prefer to transfer this responsibility to the physician, who may then choose to insert an intrauterine device or use other appropriate methods. Finally, the ideal contraceptive method should cost no more than an individual family can afford, or, if this is not entirely feasible, the cost should be within the capabilities of a government to purchase the medications if distribution on a national scale is anticipated.

Today, we have eleven scientists chosen because of their expertness in population control. They will speak on subjects of their interest, and their topics will cover different methods of contraception. Without further ado, we will ask Dr. Jaffe to discuss "Effects of Synthetic Steroids on Serum Gonadotropins."

CHAPTER ONE

Effects of Synthetic Steroids on Serum Gonadotropins:

*Determination by Radioimmunoassay**

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It has been suggested that one mechanism by which the oral contraceptives exert their effect is the inhibition of pituitary gonadotropin secretion.[1] To examine this postulate, the effects on serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) of certain synthetic estrogenic and progestational

* Portions of these studies were supported by research grants from the USPHS (NIH-HD-02929) and the Population Council.

steroids commonly employed in many oral contraceptive regimens were investigated. To study the effects of these agents, the individual components of some of the commonly employed preparations were first investigated. Subsequently, certain combination and sequential modes of treatment were studied. This study was expanded to include a continuous low dose progestin regimen (chlormadinone acetate 0.5 mgm), and the progestin, dydrogesterone, which has been reported to exert its progestogenic effect without inhibiting ovulation.

Serum LH and FSH were determined by specific radioimmunoassay techniques developed in these laboratories, which have been detailed elsewhere.[2-4] The study design was the same for each preparation investigated. Volunteer student nurses, with no detectable abnormalities in menstrual history, general physical or pelvic examination, were studied—a minimum of five subjects on each preparation studied. Most subjects obtained serum samples during a "control" month immediately before and after the month(s) of medication administration. Daily basal body temperatures were obtained during both the "control" and treatment months. In many cases, 24-hour urine samples

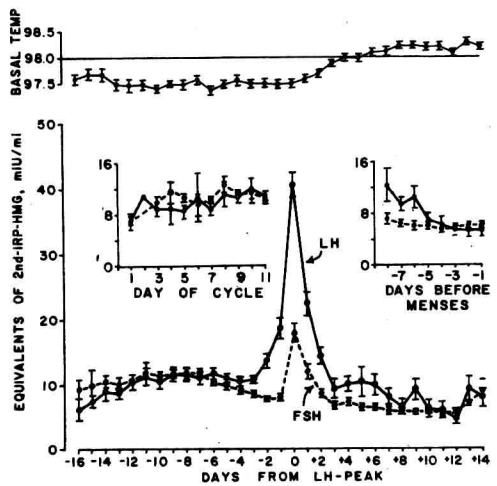

FIG. 1. Composite profile of serum LH and FSH levels throughout the menstrual cycle in 29 normal women. Day 0 = day of LH peak. Insets illustrate data from same subjects at the beginning and end of the cycles. Basal body temperature plotted above.
Vertical bars represent one standard error of the mean.

were obtained on cycle days 8 and 23 for gas chromatographic pregnanediol determinations. Serum samples were obtained alternately on cycle days 1 to 9, daily on days 11 to 23, and on alternate days from day 25 to the end of the cycle.

A composite profile of serum LH and FSH in 28 cycles in 23 women, together with basal body temperature data throughout untreated menstrual cycles, is illustrated in Figure 1. The data are plotted with the LH peak being called day 0. Data concerning LH and FSH concentrations at the beginning and end of the cycles are indicated in the insets. Basal body temperatures are plotted above.

A surge of both LH and FSH at midcycle, at about the time of presumed ovulation, can be seen. In general, lowest values are seen at the onset of menstruation, followed by a rise to fairly regular levels during the follicular phase of the cycle. Following the surge of both gonadotropins at midcycle, there is an irregular fall to lower levels during the luteal phase. Details of LH patterns during the menstrual cycle have been published.[5]

EFFECTS OF SYNTHETIC ESTROGENS ON SERUM LH AND FSH

1. Ethinyl estradiol. When 50 μg ethinyl estradiol was administered for 20 days beginning on day 5, an abolition of the midcycle surge of LH and FSH was observed, as illustrated in Fig-

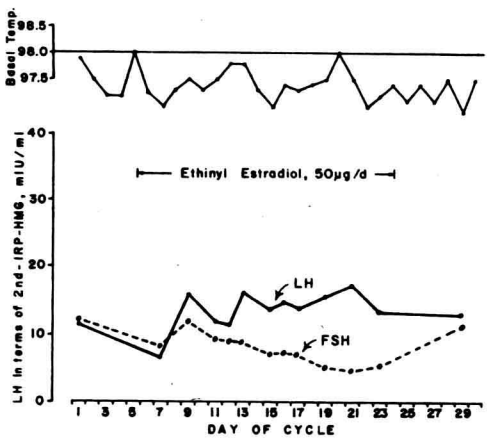

FIG. 2. Effect of daily administration of 50 μg ethinyl estradiol for 20 days on serum LH and FSH.

ure 2. There was also loss of the biphasic nature of the basal body temperature curve noted in the "control" months prior to inception of treatment.

2. Ethinyl estradiol–3 methyl ether. When Mestranol was administered in an 80 μg dose, beginning on day 5 for 20 days, an abolition of the midcycle surge of LH and FSH was again

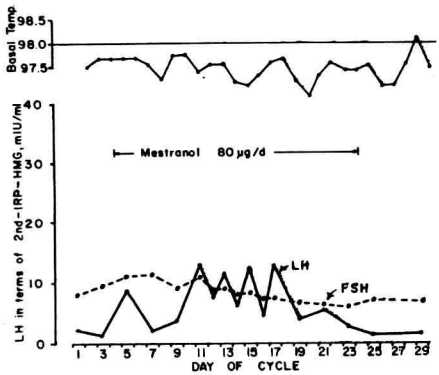

FIG. 3. Effect of administration of 80 μg Mestranol for 20 days on serum LH and FSH.

noted (Figure 3). Again, lack of a biphasic temperature curve was noted.

EFFECTS OF SYNTHETIC PROGESTINS ON SERUM LH AND FSH

1. Norethindrone acetate. When this preparation was administered by itself, 2.5 mg per day for 20 days beginning on cycle day 5, abolition of the gonadotropin surge at midcycle was observed. Vaginal spotting was a frequent side effect with this regimen. Slightly elevated temperatures were frequently observed throughout the time that medication was administered.

2. Chlormadinone acetate. Treatment of subjects for one or two months with the low dose progestin regime of 0.5 mg chlormadinone acetate resulted in loss of the normal gonadotropin profile in the large majority of the subjects. An example of the computer plotted data from one subject, with the "control" cycles plotted before and following the months of treatment, is illustrated in Figure 4. Long term studies of this preparation are now in progress.