AMERICAN LECTURE SERIES

OBSTETRICAL ENDOCRINOLOGY

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PREFACE

This monograph is made up of guest lectures given at the University of Bahia, Brazil.

I was asked to develop a monographic course in obstetrical endocrinology in only six lessons, and from the first, I foresaw the impossibility of a complete delineation of the hormonology of gestation in so short a time. However, I have tried to deal with the most prominent aspects, based on modern investigations and founded upon contributions which have extended our personal insight into these problems. A great deal of what has been said in these pages is based on knowledge solidly established at the present time, but a part, and not a small one, is still speculative. Therefore, the reading of these pages, it is hoped, will be a stimulus to meditation and also to criticism. If, with one or the other, the interest of my English-speaking colleagues is awakened in endocrinology of gestation and parturition, I will be greatly satisfied.

Bibliography is not extensive but, in each chapter, a few sources of general information are quoted wherein the interested reader will find more complete references.

Finally I have preferred to illustrate this work with diagrams, leaving out photographs and microphotographs as the former seem to be clearer than the latter.

My appreciation is expressed to Doctor Hamblen, Professor of Endocrinology, Duke University Medical Center, Durham, N. C., for his kindness in encouraging me to write this monograph. The author acknowledges his indebtedness to Doctor Ella Palma, Fellow in Gynecological and Obstetrical Endocrinology at Duke University Medical Center and presently associated with the Department of Obstetrics and Gynecology of the University of Chile (Santiago), for helping the editor with the pre-

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Madrid

JOSÉ BOTELLA-LLUSIÁ

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OBSTETRICAL ENDOCRINOLOGY

Chapter I

ENDOCRINE CORRELATIONS OF PREGNANCY— CHORIONIC HORMONES— PLACE OF FORMATION

I. INTRODUCTION

Metazoan eggs can be divided into three classes, according to their way of feeding: a) aquatic eggs, which feed on their environment; b) cleidotic eggs, which feed on reserves previously left in the protoplasm, commonly known as vitellus; c) placental eggs, which, lodged inside the maternal organism during pregnancy, are surrounded by an active chorionic membrane or trophoblast, interposed between the mother's internal medium and the fetus, procuring for the latter its nourishment.

This placental egg, lodged in the mother's internal medium, needs to adjust its ways of life within the maternal environment, but, above all, it also requires changes in the mother's body. These changes of an endocrine and metabolic nature are absolutely necessary so that the embryonic growth and transplacental nourishment can take place. This is the way in which the well known changes during pregnancy occur, originating not in the mother's organism but from ovular tissue. The egg behaves therefore, not as a saprophyte or commensal of the mother, in the ecological sense of the word, but as a real parasite. The egg, formed by the embryo and its trophoblast, is fixed inside the pregnant organism and produces through an endocrine mechanism, all those changes necessary for its bearing and nutrition.

The agents which produce these ovular changes in the maternal organism are the trophoblastic hormones. The humoral changes of pregnancy are due to the original action of these

hormones which become the initiating factors of the correlations of pregnancy.

II. ESTABLISHMENT OF THE ENDOCRINE CORRELATIONS OF PREGNANCY

In establishing the endocrine correlations of pregnancy, we must distinguish three aspects or phases: a) preimplantation period; b) nidation; and c) the chorio-maternal correlation.

a) Preimplantation Period

The physiology of the monthly corpus luteum and its influence in favoring pregnancy, by developing a bed for its implantation, are phenomena too well known today to be worthy of discussion. Fertilization takes place in a few hours or days after the formation of the corpus luteum, and, therefore, as soon as the ovum reaches the ampullar part of the Fallopian tube, the genital apparatus is already under the action of progesterone. This hormonal action is exerted, not only on the uterus, but also on the tubes. In the tubes, progesterone produces a nutritious secretion which nourishes the fertilized egg until it is fixed in the uterus.[26] In this phase there is not yet a developed trophoblast or ovular secretions which might act upon the mother's organism; in the latter there has been no change of any sort, and therefore, properly speaking, there is no pregnancy. The evolution of the egg at this primitive state is similar to that of reptiles and birds and makes one think that in these zoological species the corpus luteum would serve the same end as in the preimplantation period in humans; that is, it favors the nourishment of the non-nidated egg in its passage through the oviduct (*Fig. 1*).

Westman's experiments showed that if in a rabbit, after a fertile coitus, both ovaries were resected, the eggs would die in the tubes and would not be fertilized or implanted in the uterus. If progesterone was injected, fertilization and nidation took place in a normal way, and it has been shown in a range proportional to the dosage of the hormone injected.[9] These investigations opened the way to the supposition that the tubes under the action of the corpus luteum, develop a nourishing effect first on the ovocyte, later on the ovule and, finally, on the morula.

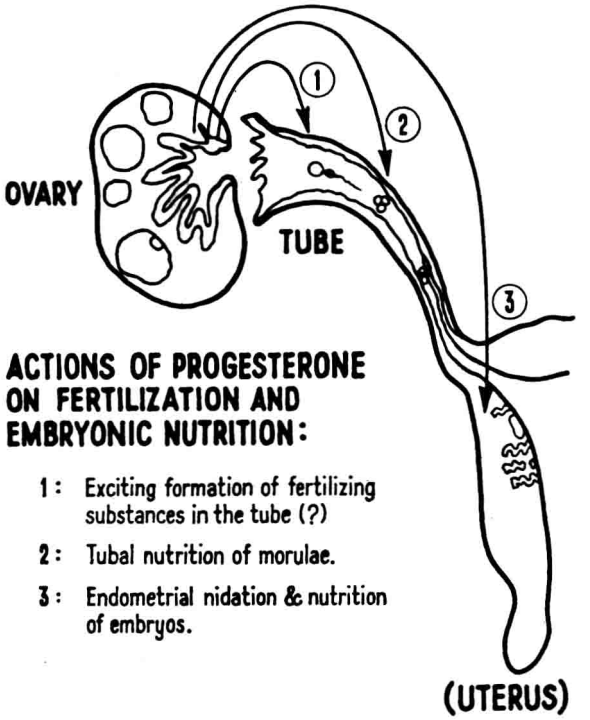

Figure 1.

Shettles[23] has shown that, without an extract from the tubal mucosa, fertilization "in vitro" is impossible. By the same token, Moricard[20] believes that the tubal flow is necessary for the dissociation of the corona radiata, and the approaching and penetration of the sperm cell. This tubal flow which favors fertilization, and probably also the feeding of the morula, is produced under the influence of progesterone. As this hormone has a stimulating effect on the oviduct flow in birds,[19] it is believed that this tubotrophic nourishment in mammals can be compared to the effect on the oviduct in birds under the influence of progesterone.

b) Nidation

In the same manner, progesterone controls the process of nidation. When the blastocyst has arrived at the uterus, it is

attracted to the mucosa for implantation by the action of progesterone. Courrier and his group[1] have shown that in rats the number of blastocysts implanted is proportional to the level of progesterone in the blood. More interesting yet are Hamlett's[16] observations on the armadillo. This animal is fertilized in autumn, but the implantation of the fertilized egg shaped in November does not take place until March; that is, it spends all winter in a fertilized state without embryonic development and nidation. There is, therefore, a lethargy in the ontogeny which coincides with a period of absence of the corpus luteum. When the latter is formed in Spring, the blastocyst, stopped in its growth, becomes implanted and starts its evolution again. This phenomenon, probably a general fact, is also found in the human species. In regard to this fact are the interesting observations of Hertig and Rock[18] who have noted that one of the most common causes of early abortion is a defective embryonic implantation. We[7] suppose that this defective implantation of young conceptus is related to a progestational insufficiency of the endometrium. The very early abortion in the human species, before the first missed period, may be very common as we have been able to show[5] and would be dependent on a deficit of progesterone.

c) Establishment of the Chorio-maternal Correlation

Pregnancy, properly speaking, starts as soon as the conceptus is implanted. At this moment differentiation of the trophoblast and secretion of gonadotropin begin. Chorionic gonadotropin (CG), although biologically and structurally similar, differs from the luteinizing gonadotropin of the pituitary (LH). Proof of small differences between them is derived from studies of the ovaries of birds. The chorionic gonadotropin (CG) is both luteinizing and luteotrophic, whereas the pituitary gonadotropin (LH) is luteinizing only and not luteotropic. Small amounts of prolactin (luteotropin) have been shown in the placenta, but it is unnecessary to explain this in order to understand why the monthly corpus luteum has a short life of eight or ten days, whereas the corpus luteum of pregnancy may last as long as three months. CG is undoubtedly secreted very early in the tropho-

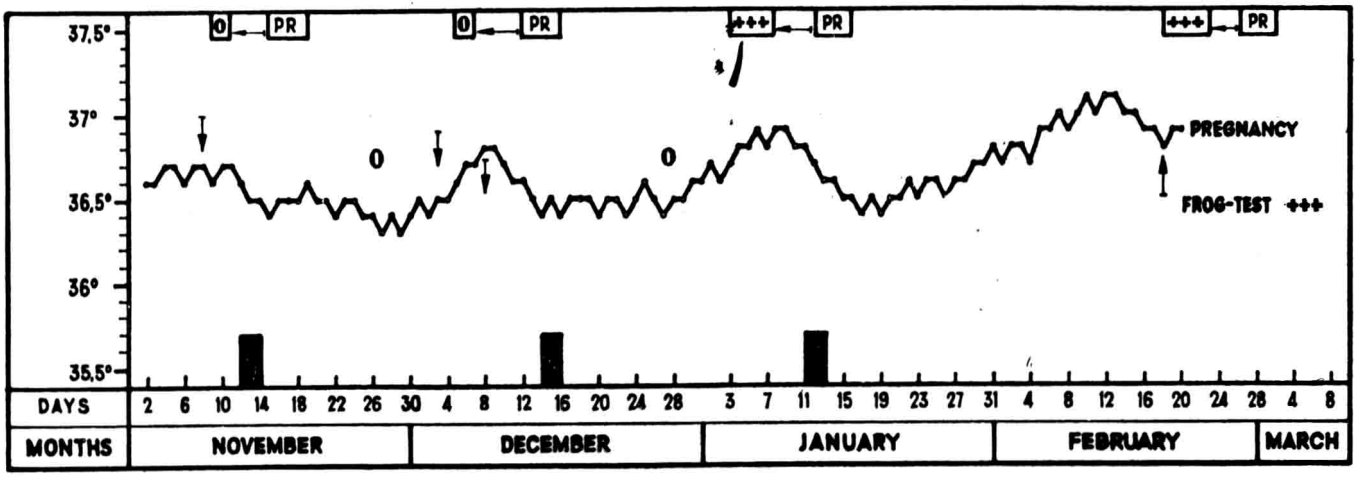

Figure 2. Basal body temperature curves of two ovulatory cycles preceding gestation. The temperature remains high during pregnancy.

blast, because so soon as the egg arrives at the uterus and is implanted, signs of persistence of the corpus luteum can be seen in the basal body temperature curves (*Fig. 2*). In many women urinary excretion of CG also can be detected early.

III. ROLE OF THE CORPUS LUTEUM IN PREGNANCY OF PRIMATES

In laboratory rodents, the correlation between trophoblastic CG, progesterone of the corpus luteum and the endometrium lasts throughout pregnancy (*Fig. 1*). In these animals resection of the ovary with its corpus luteum is always followed by abortion. If the loss of progesterone is not complete, because placentas which produce a small amount of hormone are retained, or because a small amount of progesterone is injected, then, all embryos are not expelled, and the number of them retained is in proportion to the level of progesterone in the blood.[10] Therefore, the maintenance of pregnancy in rodents is always the result of the existence of the corpus luteum in the ovaries.

In women and in apes the situation is somewhat different. We have believed for many years that the corpus luteum is, at least for the first three months, essential for the continuation of pregnancy. Nevertheless, it has been known for a long time, that pregnancy may persist after very early removal of the corpus luteum.

Our case, which follows, is illustrative:

> Mrs. Sch., twenty-seven years old. Three previous deliveries. A right ovarian cyst was diagnosed; therefore, a laparotomy was performed on Oct. 25, 1947. Last period was on Oct. 3, 1947. An orange-sized dermoid cyst was found on the right side, and another cyst, 6 cm. in diameter on the left side. A bilateral ovariectomy was performed. Because menstruation failed to occur on Nov. 15, 1947, a Friedman test was done with positive results. She delivered a living baby on June 18, 1948.

Statistics of Calatroni, Ruiz and Di Paola[9] indicate that abortion occurred in 15% of women in whom a resection of the corpus luteum was performed during the first three months, but in only 2% when the operation is done after the third month. In 1948, we[6] found two cases, in which, after resection of the

corpus luteum, values of pregnanediol were normal. Subsequent reports[22] have indicated that resection of the corpus luteum, even during the second month of gestation, does not cause abortion, the level of pregnanediol remaining normal. This proves that the corpus luteum is not essential in maintaining gestation in women, but that the production of progesterone elsewhere is indispensable. We, therefore, count upon extraovarian sources of progesterone in primates. These sources are available before the third month in 85% of the cases.

The two cases reported by us in 1948 concerned two women with ovarian cysts who were two months pregnant. In each, unilateral oophorectomy was performed. In one there was a dermoid cyst, 7 cm. in diameter, which had normal ovarian tissue in a small section of its wall and in which the corpus luteum was included. The other had a hemorrhagic cyst of the corpus luteum which was excised believing it to be endometriosis. Neither woman was hormonally treated. Postoperative determinations of pregnanediol were done and the excretion continued to be normal with a swift tendency to rise as in normal pregnancies (*Fig. 3*).

We believe that the additional source of progesterone was the chorionic tissue. Undoubtedly, the hormone is produced in

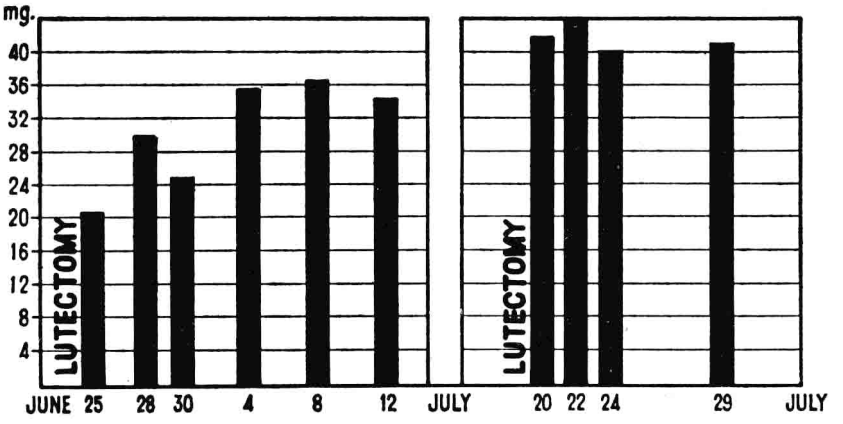

Figure 3. Two cases of resection of the corpus luteum in the second month of gestation. In both instances gestation continued with a normal excretion of pregnanediol.

early placentas. However, in the case of Mrs. Sch., it is hard to believe that the trophoblast produced progestogen so early. Another source of progesterone capable of producing the hormone in sufficient amount to maintain gestation, could be the adrenals. It has been demonstrated[17] that adrenal perfusion in dogs with cholesterol C-14, identifies the presence of radioactive progesterone in the efferent blood vessels. The old suggestion that the adrenal cortex produces progestogens thereby has been demonstrated. Probably, progesterone is an important link in

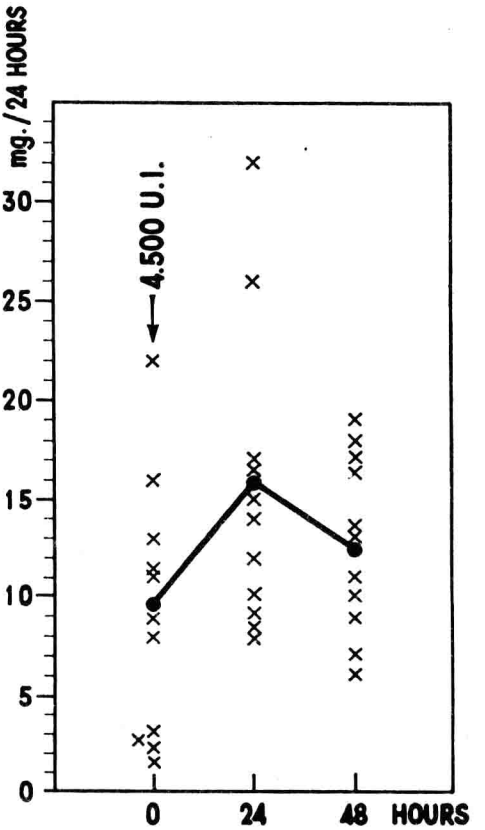

Figure 4. Action of 5,400 I.U. of chorionic gonadotropin (CG) on the pregnanediol excretion in the urine of a surgically castrated woman. The rise proves that progesterone is secreted by the adrenals. (Botella-Llusiá, J.: *Arch. Gynak.*, *183*:75, 1953.)