Uterine Contraction—

SIDE EFFECTS OF STEROIDAL CONTRACEPTIVES

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Series Preface

This volume represents the first of the Wiley-Interscience Series, *Problems of Human Reproduction*. Our aim is to insure that each volume of the series will focus on one or two current research breakthroughs in reproductive physiology which bring mankind closer to its dual goal of controlling the overflow of our species while still making provision for care of our offspring. Thus specialists in fields of basic biology, the health professions, and the social sciences will be exposed to newer methods brought to bear in understanding both the normal processes of control and nuture of population, as well as techniques that man can utilize to alter these processes.

The need for such a series has arisen because of the methodologic specialization that has arisen in the areas of population control and fetal and child health. Thus many journals, individual monographs, and book series are devoted to purely clinical aspects on the one hand, and to basic biology on the other, with little mix of the two. Most publications cover only those aspects studied by a particular morphologic, physiologic, or biochemical approach. The editors of this series wish to expose readers from a wider range to current problems in reproduction. Although the editors wish to make a considerable body of scientifically proven information available to the reader, they are not afraid to reveal the discrepancies and implications of such a variety of approaches to problems, or to acknowledge that many theories or facts remain to be described. For, as noted by Lucretius:

> ". . . know thou that there exists
> In nature bodies which e'en thou thyself
> Must needs confess having being, though unseen"

(*Rerum Naturae*, I: 268)

JOHN B. JOSIMOVICH

June 1972

Preface

The first volume of the Wiley-Interscience Series, *Problems of Human Reproduction*, presents two topics that are receiving considerable attention in the current technical literature and in the news media: Natural and artificial control of expulsion of the uterine contents, and the side effects of the oral contraceptives upon the bodily physiology of the user.

For consideration of the first topic, The Control of Uterine Contraction, chapters by the Editor and by Dr. Braaksma and colleagues first consider problems in the measurement of physical forces acting upon the uterus and within the uterus itself. Further review of the approaches to the study of the pharmacologic control of uterine electrical activity is given by Drs. Daniel and Lodge, the manner by which the autonomic nervous system effects uterine contractility by Dr. Moawad, and review of the problems in measuring oxytocin in the context of uterine contraction by Drs. Munsick and Glick. Experimental evidence for the importance of circulating concentrations of estrogens and progestins in both inhibition and potentiation of uterine contractions is given by Dr. Hein and colleagues, and by Drs. Johannson and Holmdahl. The role of the prostaglandins in the natural and artificial induction of labor is of vital current interest for purposes of induction of premature expulsion of uterine contents before or soon after embryonic implantation, as well as in the induction of labor in term pregnancy. The effects of the prostaglandins on uterine muscle is described by two of the outstanding groups contributing to our knowledge of this subject: Drs. Karim and Hillier, and Drs. Bygdeman and Wiqvist. Chapters by Dr. Levitt and by Dr. Kirton review the chemistry and biochemical background for our understanding of these ubiquitous chemicals. Drs. Liggins and Chez have contributed further chapters on recent studies by themselves and others indicating roles of the fetal endocrine glands in determining the onset of labor. Finally, an integrated view of these numerous factors is presented in the form of a review of personal laboratory studies by Dr. Csapo. The final three chapters of the first

section are devoted to external control of these basic physiologic processes: bacterial infection (Dr. Driscoll); pharmacologic control of autonomic nerves and pathologic uterine activity (Dr. Eskes); and the mechanisms by which alcohol administration may inhibit labor (Drs. A.-R. and F. Fuchs).

The second topic of Volume 1, Side Effects of Steroidal Contraceptives, is initiated by a general review and by a description of possible adverse effects, after discontinuation of "the pill," on the physiologic control of ovulation and fertility by Drs. Charles and Rankin. Doctor Spellacy then reviews the effects of the oral contraceptives on carbohydrate metabolism in the normal person and in the diabetic. A chapter by Doctors Gonzalez-Angulo and Salazar concludes with a review of the effects of these agents on the morphology of female reproductive organs and discusses the possible carcinogenicity indicated by these structural alterations.

The Editor wishes to thank his assistant editors, Dr. B. N. Saxena of the World Health Organization, Bangkok, Thailand, and Dr. P. G. Crosignani of the University of Milan, Milan, Italy, for their advice in organizing the series. The Editor also appreciates the encouragement given him by Mr. Alan Frankenfield, Editor of the Biologic and Medical Sciences, Wiley-Interscience Division of John Wiley & Sons, and for the facilities of Dr. Donald L. Hutchinson, Chairman of Obstetrics and Gynecology, University of Pittsburgh School of Medicine, as well as the help in manuscript preparation by Mrs. Katherine Meinzer of the Department of Obstetrics and Gynecology.

JOHN B. JOSIMOVICH

Pittsburgh, Pennsylvania
June 1972

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PART ONE: THE CONTROL OF UTERINE CONTRACTION

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Physical Forces Acting upon the Gravid Uterus

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In the transition of the nongravid uterus to the rapidly growing organ of pregnancy, the closing off of the internal cervical os by the fetal membranes creates the possibility of an intrauterine pressure differing from that found in the atmosphere. Unquestionably, one of the primary marvels of gestation is the ability of the uterus to grow without any large increase in muscular tension. Much of this process of initial hyperplasia and hypertrophy of the myometrium, with a sudden conversion from a spherical to an elliptical myometrial mass surrounding each conceptus, has been carefully documented in certain species by Reynolds in his monograph on uterine physiology (1). It is the purpose of this chapter to raise further questions about the precision of measuring the outward pressure on the myometrium exerted by the conceptus and pressures directed from without by the abdomen, along with a brief duscussion of the consequences of such considerations upon our understanding of maternal-fetal exchange. Figure 1 schematically represents the opposing pressures acting on a unit area of

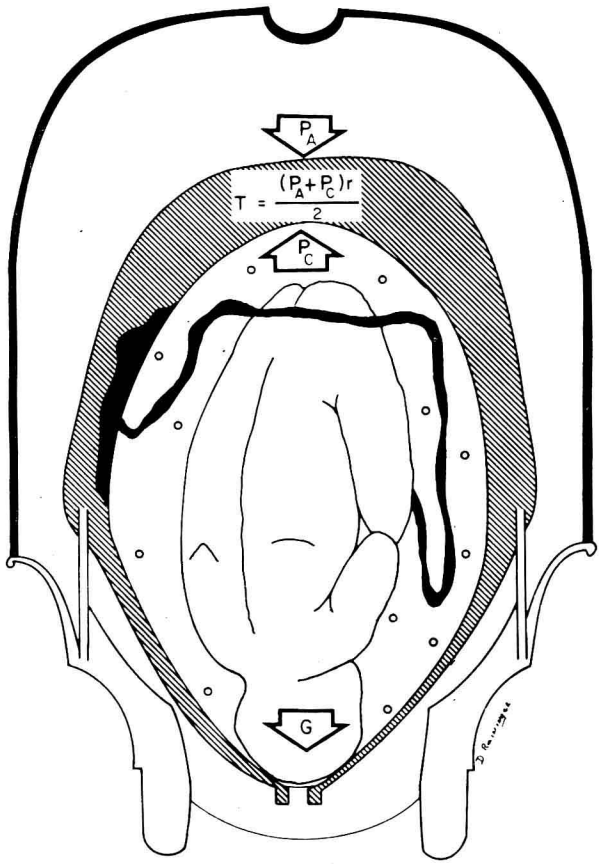

Figure 1. Myometrial tension as a function of the radius of a curvature (*r*), assuming a spherical shape. The tension (*T*) is proportional to the difference between the opposing pressure vectors of intraabdominal pressure (P_A) and that produced by the conceptus and amniotic fluid (P_C). G is force of gravity.

the uterine wall. The sum of the opposing vectors, P_A and P_C, gives the net pressure from which the tension, T within the wall, may be determined. Thus $T = (P_A + P_C)r/2$, a corollary of Laplace's law as modified for the spherical fundus by Reynolds and his predecessor, Haughton (1). At the outset, it should be pointed out that the P_C, P_A, and *intramyometrial pressure* are assumed to be the same at equilibrium, due to the elasticity of the uterine and abdominal walls. As will be pointed out, however, slight differences in pressure due to imperfect elasticity of uterine and abdominal

walls might lead to profound physiologic disturbances in fetal nutrition. The possibility of such inequalities, be they brief in duration, requires that this chapter emphasize the need for separate analysis of the external and internal forces which may act against one another to insure that intramyometrial tension remains at a minimum.

INTERNAL FORCES

Although detailed studies of intrauterine pressure have been made between contractions during labor (2–4), measuring pressures of approximately 5–15 mm Hg, little has been recorded in early primate pregnancy. Ramsey has shown that low pressures were recorded by her group and by that of Hendricks in rhesus monkeys and women earlier in pregnancy (5). One systematic study in early mammalian pregnancy of changes in intrauterine pressure was that carried out by Reynolds in the rabbit (1). In that species an increasing pressure was noted at a time when the growth of fetus and surrounding fluid-filled membranes exceeded the accommodation provided by the hypertrophy and hyperplasia of the myometrium. With a sudden "conversion" in shape of the myometrium surrounding a conceptus (and consequent thinning of the myometrium from rearrangement of the syncytium) there was a decrease in intraamniotic pressure which was maintained in the latter part of pregnancy. Clearly, the elasticity of the myometrium is the main reason for low intrauterine pressures so far recorded. It has been clinically recognized for many years that even uterine overdistention from hydramnios does not usually increase intrauterine pressure.

According to Reynolds (1), the studies of Haughton carried out on the human uterus showed that because of the greater radius of curvature in the fundus in late pregnancy, Laplace's law would predict that the pressure exerted by the intrauterine contents should cause twice as much tension to develop in the fundal myometrium as would be expected in the lower segment. Reynolds went on to question whether the greater thickness of the fundal myometrium might not be stimulated by the greater tension of the upper pole of the human uterus.

In late pregnancy the force of gravity acting upon the fetus when the mother assumes an upright posture also exerts increasing pressure on the lower uterus. Such a force becomes important during labor.

EXTERNAL FORCES

Much has been written of the pressure which the pregnant uterus may exert upon certain structures of the body (e.g., diaphragm, right ureter,

inferior vena cava) and the physiological consequences. Clinical experience dictates that the abdominal boundaries, because of their elasticity and contents, exert only a slight force upon the uterus except during bearing-down in the second stage of labor. Even before bearing down, however, there is reason to believe that abdominal wall tension contributes to positive intrauterine pressure. In a classical paper on intrauterine pressure recording, Woodbury and colleagues (4) showed that an intragastric balloon gave pressures of 5 or more mm Hg which they could subtract from total intra-amniotic pressures by measuring the pressure difference across a diaphragm between two chambers connected by catheters to the intragastric and intrauterine balloons. Using more sophisticated pressure recording devices, it would be interesting to know the exact magnitude of the intraabdominal pressure in an erect or recumbent female in order to determine P_A in Fig. 1, and whether such pressure varies between individuals of different height. The component of pressure recorded through intrauterine catheters or balloons by more recent workers contributed by extrauterine pressure thus often remains to be defined. The maintenance of a low intraabdominal pressure must result in large part from the almost isotonic stretching of such muscles as the Rectus abdominis. The phenomenon of this skeletal muscle's adaptation remains to be described by comparative measurements as pregestational and term pregnant resting length. In any event, tension within the myometrium is undoubtedly kept at a minimum by the elasticity of the uterine wall on the one hand, and by the elasticity of the abdominal wall on the other.

In contrast to such a positive contribution to intraamniotic pressure, decreases in intraabdominal pressure shown by Hendricks (6) *during* intrauterine contractions suggest imperfect elasticity of the abdominal wall. Otherwise there need not be a temporary increase in extrauterine intra-abdominal volume resulting in a pressure decrease.

Once bearing-down begins at the end of the first stage of human labor, there is clearly an increased pressure on the uterus, which is transmitted to the intrauterine contents, as was shown by many workers, including the early study of Woodbury and coworkers (4). Evidence of the importance of skeletal muscle work in the expulsion of the fetus may be inferred from clinical situations in which bearing-down is affected by certain medications. Figure 2 demonstrates that the length of second stage in 102 primigravida delivered by the author at the Boston Lying-In Hospital, Boston, and at Magee-Womens Hospital, Pittsburgh, varied when the involuntary bearing-down was altered by certain sedation regimens. Of the 65 patients sedated with scopolamine and secobarbital, 19 required more than 1½ (6 quarter) hours, while only 2 of 37 patients given small doses of narcotics required more than 1½ hours. Low spinal anesthesia was immediately

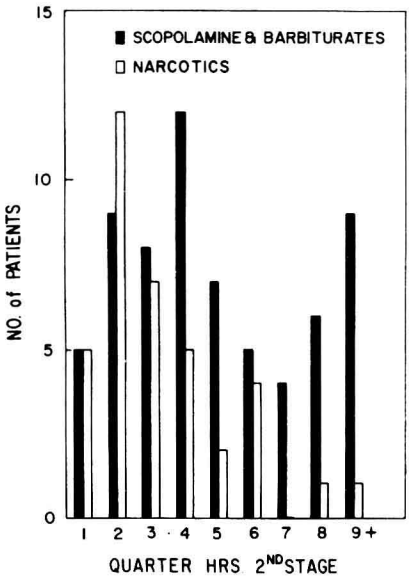

Figure 2. A comparison of the length of second stage of labor in primigravidas given scopolamine-barbiturate sedation and narcotic analgesia. Differences may be seen in the frequency of second stages of greater than 1½ (6 quarter) hours.

available for delivery in all cases. The mean age of patients receiving scopolamine and barbiturates was 21.7 years, with a standard deviation of 2.0, while the mean age of those receiving narcotics was 23.4 $\pm$1.8 years. No great differences in socioeconomic class were noted between the two groups. Two patients in each group were non-Caucasians. A chi-square test on the significance of the difference in proportion of each treatment group requiring more than 1½ hours second stage gave a highly significant P value of less than 0.01.

SIGNIFICANCE OF SEPARATE DETERMINATION OF INTRA- AND EXTRA-UTERINE PRESSURES

In their studies on blood flow in muscular limbs, Burton and Yamada (7) described a "critical closing pressure" in which they postulated that blood flow could cease due to blood vessel collapse when small arterial pressure fell to a certain level, for instance at 25 mm Hg in the human forearm. The "critical closing pressures" in the arteries supplying the myometrium, and for the spiral arteries entering the intervillous space of the placenta, remain to be determined. The classic cinemaradiographic studies in the rhesus

monkey carried out by Ramsey and Harris (8) showed abolition of arterial inflow into the intervillous space when contractions stimulated by oxytocin administration caused intraamniotic pressure to reach 36 mm Hg. If one were to subtract the intraabdominal pressure, the transmural pressure [$(P_A + P_C)$ in Fig. 1] would be 36 mm Hg minus the intraabdominal pressure, P_A, or perhaps as low as 25 mm Hg. Thus it would appear again that separate determinations of extra- and intrauterine pressure would be valuable for an understanding of how small a transmural pressure difference might occlude blood flow. Only then could investigation be made of the increase in arterial tone needed to counteract vascular occlusion. Simultaneous measurement of intra- and extrauterine pressure during the influence of vasoactive drugs might reveal that changes in arterial tone would alter the "closing pressure" as has also been demonstrated in the forearm by Burton and Yamada. Hendricks and colleagues (9) have demonstrated that the total intramyometrial pressure is not significantly different from the intrauterine pressure. It must be remembered, however, that even the knowledge of the effects of transmural pressure changes will not finally solve all questions of normal and pathologic alteration of small artery blood flow: Transmural pressure differences may be more or less effective in altering blood flow depending on the direction of arterial traversement of the muscle (a spiral configuration tending to minimize the effects of pressure parallel to the endometrial surface). Furthermore, segregation of total intramyometrial pressure into localized pressure differentials such as apparently exists in the interstitial fluid surrounding vessels, as discussed by Guyton and his colleagues (10), may well alter the forces acting on the spiral arteries of the uterus.

One further consequence of the elasticity of the myometrium is the prevention of excessive diffusion of substances from the amniotic fluid to the maternal uterine circulation. According to recent *in vitro* studies (11), human chorionic somatomammotropin appears capable of passing across the human chorion and amnion by diffusion as readily in one as in the other direction. A driving force for passage of this substance of approximately 22,000 molecular weight into the amniotic fluid is undoubtedly the higher concentration in the uterine arterial blood. If intraamniotic pressure should rise more than intraabdominal pressure, however, from lack of uterine elasticity, greater diffusion from amniotic fluid to maternal arterial blood might be temporarily favored.

It is hoped, therefore, that studies of uterine contraction and tone outlined in the rest of this volume will also be considered for their possible effects on fetal nutrition.

ACKNOWLEDGMENTS

The author wishes to thank Dr. Howard Turner of the Schools of Medicine and Public Health, University of Pittsburgh, for the calculations of standard deviation of the ages of patients depicted in Fig. 2; the Medical Arts Department of Magee-Womens Hospital for the figures; and Dr. Franklin Fuchs of the Department of Physiology for his valuable suggestions.

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2

Digital Evalution of Uterine Contraction Records

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The most controversial problems centering around the accuracy of pressure recording in the uterus *in vivo* seem to be the accuracy of different pressure recording techniques (1–3), the consistency and variability of myometrial contraction patterns (4–6), and the consistency of interpretation of the records qualitatively (7) and quantitatively (8). For precise quantitative interpretation of the results, accurate computed parameters are needed, parameters which reflect exactly the process that is investigated: the contraction of the myometrium.

A large variety of parameters is used to compute the records that are obtained from the nonpregnant or the pregnant uterus *in vivo* (Fig. 1):

- Intensity (amplitude), frequency (interval), and duration of the contractions.