Maternal Vascular Compliance of Placentas in Rabbits

Gwen Matthews Brownfield

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ABSTRACT

MATERNAL PLACENTAL VASCULAR COMPLIANCE IN RABBITS

by Gwen Matthews Brownfield

The incidence of maternal and infant morbidity and mortality has led to a continued study into the physiology and pathophysiology of the placenta, the seat of life for the developing fetus. For several decades investigation has been made into the morphology and exchange functions of the placenta and blood flow in the uterus and placenta, but only recently has compliance begun to have been studied. Recognizing the important part it plays in affecting circulation, compliance has been studied in the fetal circulation of the placenta, the fetal placental vascular bed, and the umbilical vasculature. The purpose of the present study was to determine maternal placental vascular compliance.

Through ethical considerations, the study was carried out on 20 anesthetized near-term New Zealand white rabbits, as their placental structure is similar to that of humans. Erythrocytes and plasma were labeled with $^{51}\text{Cr}$ and $^{125}\text{I}$ in order to determine placental maternal blood volume. Maternal pressure was measured by means of catheters placed in femoral arteries and veins and recorded on a plethysmograph. Adjustable ties were placed around the maternal inferior vena cava and aorta so that pressures could be altered. A fetus with its pla-
centa was snared at four different pressures, the order being randomized: one at normal, one with the aorta fully occluded, one with the aorta partially occluded, and one with the inferior vena cava occluded. Whole placentas were placed in vials for isotope counting by a gamma well counter, and plasma, erythrocyte, and whole blood volumes determined. Intervillous space pressure was estimated from maternal arterial and venous pressures assuming a venous to total resistance ratio of 0.02. The pressure-volume relationship in the placenta was plotted, and compliance was calculated from the slope of the curve.

At normal maternal arterial \((P_a)\) and venous \((P_v)\) pressures of 71.8 and 5.5 mm Hg, placental blood volume was 0.447 \((\pm 0.051 \text{ SEM})\) ml/g placental tissue. When venous pressure was raised \((P_a = 45.5, P_v = 12.2 \text{ mm Hg})\) by occluding the inferior vena cava, blood volume increased to 0.729 \((\pm 0.068 \text{ SEM})\) ml/g, a significant 63 percent rise. However, when arterial pressure was lowered by occluding the aorta in two steps, dropping to \(P_a = 33.8, P_v = 7.0\) and \(P_a = 13.5, P_v = 5.4\), volume did not decrease significantly. Over the intervillous space pressure range from normal to high, placental compliance was 0.0471 ml/mm Hg/g placental tissue. The results suggest that maternal placental volume would be maintained during transient hypotension and would increase when venous pressure is elevated.

A sidelight from the study was that maternal placental hematocrit averaged 27 percent, appreciably less than the circulating hematocrit of 38 percent, possibly due to plasma skimming where erythrocytes are directed preferentially into faster flowing streams. The rise in hematocrit seen when the inferior vena cava was occluded may have been
due to increased blood vessel diameter and slower flow with consequently less preferential erythrocyte distribution and plasma skimming. The low placental hematocrit indicated that erythrocytes transit the placenta faster than plasma, a finding that may have implications for gas exchange.

The results reveal the placenta to be a very compliant organ under normal conditions, with a structure that provides for maternal-fetal exchange under a variety of pressures. The findings lend support to the nurse in the clinical setting in reassuring the concerned mother-to-be of her body's adaptation and resilience under normal circumstances in providing for the developing fetus. The study lays a foundation for further study into how compliance may be affected in certain disease states and conditions that make pregnancies high risk.
MATERNAL VASCULAR COMPLIANCE OF PLACENTAS IN RABBITS

by

Gwen Matthews Brownfield

A Thesis in Partial Fulfillment
of the Requirements for the Master of Science Degree
in the Field of Nursing

November 1979
Each person whose signature appears below certifies that he has read this thesis, and that in his opinion it is adequate, in scope and quality, as a thesis for the degree of Master of Science.

Clarice W. Woodward, Professor of Nursing

Gordon G. Power, Professor of Medicine

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Chapter 1

THE PROBLEM

Many physiologic and pathophysiologic aspects of pregnancy and labor have baffled and continued to puzzle those concerned with obstetrics. An understanding of some complex problems is possible only as the mysteries of the structure and function of the placenta, the basic unit of fetal-maternal exchange, continues to be studied.

Background and Statement of the Problem

The well-being of mother and baby have been the focus of medicine and nursing for centuries. As technological abilities have expanded, the growth of intensive care nurseries, neonatal regional care facilities, and special monitoring of mother and baby even before birth has been observed. However, the incidence of maternal and infant morbidity and mortality continues to higher than desirable and has stimulated further inquiry and study into pregnancy, labor, and delivery. High risk is involved especially in certain disease states complicating pregnancy, and an understanding of the physiology and pathophysiology of the placenta is vital to improved care of mother and baby.

It has been found that the function of any organ in the body is determined by its structure, and the placenta is no exception. The diffusion of various gases between the maternal and fetal circulations which is so critical to fetal well-being is dependent upon the structure
of the placenta. The intervillous space is a sealed chamber into which blood enters from maternal arteries. The placental fetal villi are in contact with this pool of maternal blood. An exchange of gases, wastes, and nutrients takes place between maternal and fetal circulations as the maternal blood in the intervillous space bathes the villi which are anchored to the basal plate. Much investigation has already been done into the exchange functions of the placenta, the blood flow in the uterus and placenta, and the morphology of the placenta, but at present, the compliance of the placenta had not been determined.

**Purpose of the Study**

The purpose of this study was to determine the compliance of the maternal side of the uteroplacental unit in rabbits. This could lay the groundwork for further study into how disease states may affect the compliance of the placenta and thus the exchange between the mothers and fetus.

**Design and Methodology**

The study was conducted using a true experimental design. The data collection method used was to label erythrocytes and plasma for the purpose of measuring the volume of maternal blood in the placenta at different maternal blood pressures. Calculations of the blood volumes were normalized to 1 g of placental tissue and corrections were made for background, hematocrit ratio, and the Compton effect. Compliance was expressed in terms of ml of blood per mm Hg per g placental tissue. Further details of the methodology are found in Chapter III.
The research facilities of the Loma Linda University Medical Center were used to carry out the study on twenty-seven anesthetized rabbits that were near-term. It was assumed that each mother served as her own control.

Delineation of the Research Problem

The physiological compliance of an organ refers to the relationship between volume change and pressure change. If the compliance is low, a very small change in volume could make the pressure rise to dangerous levels.

The structure, shape, temperature, and composition of the organ determines its compliance. This could have implications for conditions which alter any of the foregoing. For instance, diabetes exhibits changes in scleroproteins in various parts of the body with a resulting decreased compliance in lungs and blood vessels.

Questions to be answered were: (1) Is the placenta also affected? (2) Are the pressure-volume relationships changed in certain disease states? Before compliance is measured in pathologic conditions it is important to know what the compliance is under normal conditions.

Theoretical Framework

The placenta as an organ of maternal and fetal origin functions in the exchange of gases, nutrients, and waste products and is therefore vital to fetal well-being (langman, 1975).

The exchange of nutrients, gases, and wastes is dependent upon the volume of maternal blood in contact with fetal villi (Brinkman,
The volume of an organ is limited if the organ is not distensible (Schuyler, Niewohner, Inkley, and Kohn, 1976; Wisneski and Bristow, 1978) or in certain disease states (Ganong, 1975; Mirsky and Parmley, 1973). In the normal uncomplicated pregnancy, the placenta functions adequately to provide for the developing fetus through this exchange of nutrients, gases, and wastes (Comline and Silver, 1974; Venuto, Cox, Stein, and Ferris, 1976; Warwick and Williams, 1973).

If the preceding statements are indeed true, then the placenta under normal conditions must be a very compliant organ so that a change in blood volume is not accompanied by a great change in blood pressure. The hypothesis stated in the null was: There will be no change in the blood volume given a change in maternal pressure. Pre-set level of significance was alpha = .05.

Traditionally, nurses have functioned primarily in direct patient care, administration, or in teaching, but nursing's contribution need not be limited to these areas. As part of the larger world, nurses concerned with the well-being of mother and baby can also be involved in primary scientific research that builds basic foundations of knowledge in physiology from which patient care and teaching stems.

Limitations

Because of obvious ethical barriers of using human subjects, the study was limited to determining compliance in the placentas of rabbits.
Although compliance of the rabbit placenta cannot be assumed to be the same as compliance of the human placenta, findings from this study can lay a foundation for understanding the dynamics of pressure-volume relationships in the human placenta, as placentas of the two species are similar in structure (Abitbol, Driscoll, and Ober, 1976; Venuto and others, 1976).

The actual ratio of arterial to venous resistance in the utero-placental unit of the rabbit has not been measured accurately and so the findings from studies in monkeys were used in calculating pressure in the intervillous space. Further details of this are reported in the discussion section of Chapter III.

A third limitation of the study was that the effect of possible variance in the shape of the placentas at the higher blood volumes on compliance was not taken into account.

Due to ethical considerations, the study was conducted using anesthetized animals. Ladner, Brinkman, Weston, and Assali (1970) did not observe any deleterious effects when sodium pentobarbital rather than local anesthesia was used in ewes whose uterine circulations they were studying. However, Comline and Silver (1974) point out that it is not yet known to what extent any anesthesia may alter the distribution of blood flow in the uterus and placenta.

**Definition of Terms**

Physiologic compliance sometimes referred to as distensibility, is the index referring to the change in volume per unit change in
pressure and generally follows a curvilinear relationship in most biological materials (Mirsky and Parmley, 1973).

The maternal component of the uteroplacental unit in this study refers to the sealed chamber containing maternal blood that bathes the fetal villi.

Blood volume of the placenta was measured using radioactive isotope labels to determine erythrocyte, plasma, and whole blood volumes of whole placentas placed in a gamma well counter.

Maternal pressure was measured by means of catheters placed in the femoral artery and vein of each pregnant rabbit and were recorded during the experiment by means of pressure transducers and a plethysmograph.

The Thesis

The remainder of the study follows, beginning with a review of the related literature in Chapter II. The structure and function of the placenta, the concept of compliance as it has been studied in other organs and systems of the body, and the effect of labor and certain pathologic conditions on the placenta and thus the fetus are included.

The third chapter consists of the article submitted for publication dealing with this investigation into the compliance of the maternal component of the uteroplacental unit in rabbits.

A summary, conclusions, recommendations, and implications for nursing that arise from the study comprise the final chapter.
Chapter 2

REVIEW OF THE LITERATURE

The review of the literature done in 1975 covered three areas: (1) the function and structure of the placenta, (2) the area of physiologic compliance in order to gain an understanding of the concept and what methods have been used in its study, and, (3) how the placenta and fetus are affected by various conditions in the mother. The final section is a review of the literature pertinent to the study published between 1976 and 1978.

The Function and Structure of the Placenta

The placenta is an extremely complex organ performing a variety of functions essential to the developing fetus. Oxygen and nutritive materials are taken up by the fetal blood and carbon dioxide and fetal wastes are discharged into the maternal circulation in a fashion analogous to exchange in the lungs (Ganong, 1975). A great deal of research which is too voluminous to deal with adequately here has centered in this exchange of gases and other materials.

Because of the emphasis on its role in the exchange of gases and other materials, it might be easy to overlook other important functions of this vital organ. For example, the transport of glucose and amino acids to the growing fetus was an area studied by Widdas (1961). The placenta is also involved in the maintenance of osmotic equilibrium be-
between maternal and fetal circulations, the modification and elaboration of hormones, and the actual production of certain important hormones in pregnancy (Guyton, 1974).

Among species, the structure of the placenta varies more than any other organ (Wynn, 1968). In man, rabbit, guinea pig, rat, mouse, and baboon the small units called cotyledons are combined to form a single flat plate. In the cat and dog a narrow band encircling the fetus comprises the placenta. In the sheep, goat, and cow, between 30 and 80 cotyledons are dispersed across a wide area of the uterus (Dawes, 1969).

Placentas are classified into types on the basis of the number and type of tissue layers interposed between the maternal and fetal bloods (Baur, 1977; Warwick and Williams, 1973). In 1909, Grosser originally described epitheliochorial placentas as those in which all layers are present. Syndesmochorial placentas lack the maternal surface epithelium. Endotheliochorial placentas have only the endometrial vessel walls present, while hemochorial placentas lack even these, so that the chorionic villi are bathed in maternal blood. In 1952 Amoroso added the hemoendothelial placenta to the list. In this type, the chorionic trophoderm is absent as are the maternal tissues, leaving a structure in which only the fetal capillary walls lie between the maternal and fetal circulations. In recent years there has been concern that this original classification may not be adequate (Ludwig, 1972). Wynn (1968) was concerned that there was danger in rigid classifications neglecting differences in origin, function, and even histological transi-
tions within the same placenta. However, Dawes (1969) pointed out that although the Grosser classification is of uncertain value, it has yet to be replaced by a better system of classification.

The structure of the placenta varies not only between species, but within a single species during gestation may change its histologic classification. For example, in the last days of gestation in the rabbit, the placenta which has previously been epitheliochorial becomes predominantly hemoendothelial (Amoroso, 1952; Samuel, Jack, and NathanIELSZ, 1975). In the human placenta, the terminal villi become smaller with gestational age while the capillaries within each villous increase in number and come closer to the surface of the villous wall most likely to facilitate transfer of materials and gases. Physiologic changes in the uteroplacental vasculature allow for much greater blood flow into and through the placental intervillous space by reducing the peripheral vascular resistance in the placental bed (Moll and Herberger, 1975).

But even these alterations do not make the transfer of gases as efficiently as in the lung. In the most favorable situation, an oxygen molecule must detach from a maternal hemoglobin molecule and then pass consecutively through the intracellular fluid and membrane of the maternal erythrocyte, plasma, syncytial trophoblast, basement membranes, endothelium of the fetal capillary, plasma, the membrane and intracellular fluid of the fetal erythrocyte and finally combine with the fetal hemoglobin molecule (Laga, Driscoll, and Munroe, 1973).

Guilbeau and Knisely (1972) pointed out that the placenta is a unique organ composed almost entirely of vascular elements, having both
fetal and maternal components. The primary functional unit of the fetal portion is called the fetal cotyledon and consists of a tree-like structure where the main stem villous has many branches and has its "roots" in the chorion. The smallest branches are the terminal villi which are bathed by maternal blood flowing in the space between the villi, called the intervillous space (Martin and Gingerich, 1976).

The maternal component of the uteroplacental unit consists of the intervillous space and the decidual plate from which connective tissue septa arise (Jacob and Francone, 1974; Langman, 1975). Spiral arterioles bring blood from the endometrial branches of the uterine arteries to the maternal side of the uteroplacental unit through the basal plate and open into the intervillous space (Langley and others, 1974; Parer, 1976). The intervillous space emerges as such around the fourth month of gestation from the isolated lakes of maternal blood early in pregnancy. Reynolds (1972) likened this to the process of pockets of gas fusing in aging cheese. In the fully developed normal placenta, there are an estimated 60 villous stems from the chorion (Warwick and Williams, 1973) and approximately 100-150 spiral arteries opening into the intervillous space (Brosens and Dixon, 1966). Endometrial branches of uterine veins carry the blood away through complex drainage connections with abundant intercommunications to minimize the possibility of obstruction to venous drainage.

As in many areas of research, investigators are not all in harmony even on the structure of the placenta. For instance, there is some disagreement about whether the human placenta has a single villous
stem and one maternal arterial ostium supplying each lobule or whether one stem supplies several lobules (Gruenwald, 1966; Papalia-Early and Gruenwald, 1976; Reynolds, 1972). Some examples of other areas that have been studied are the effect of pregnancy hormones on tissues (Robertson, 1976), adaptations of vessels in the hypertrophy of the uterus (Reynolds, 1972), and the dynamics of uteroplacental circulation (Greiss, 1966; Ladner and others, 1970).

**Compliance**

Compliance is a term used to describe stretchability or distensibility. It is the index referring to the change in volume per unit change in pressure and generally follows a curvilinear relationship which is usually exponential in form in most biological materials (Mirsky and Parmley, 1973).

Compliance is determined by the composition and structure of the organ or system. For instance, the unusual nature of the pressure-volume curve of blood vessels where the greater the stretch the greater the resistance of the vessel wall, is due to the heterogeneity of elastic and collagenous fibers composing the wall. Aging is accompanied by an increase in the total number of collagen fibers in the blood vessel wall and a tightening up of these fibers so that they are brought into action by a much smaller degree of stretch in the wall (Burton, 1962). Romero, Covell, and Friedman (1972) took into consideration the influence of other factors as well, such as temperature, geometry, and pressures exerted from surrounding structures when they studied
comparative pressure-volume relations of the fetal, newborn, and adult hearts in sheep.

Along with these physiologic factors, disease has been seen to have an impact on compliance. Several investigators have noted that left ventricular compliance is decreased in the presence of coronary artery disease, angina pectoris, and acute myocardial infarction (Diamond and Forrester, 1972; Ekong, Pizzada, Vokonas, and Hood, 1972; Wyatt, Forrester, Tyberg, Goldner, Parmley, and Swan, 1972). The rigidity of the lungs or chest wall increases with pulmonary fibrosis, pulmonary congestion, and airway obstruction, thus lowering compliance (Ganong, 1975).

Various methods have been employed in the study of compliance. Rothe and Drees (1976) used hemorrhage to study the relationship of vascular pressure to blood volume in dogs. They calculated vascular stiffness as the ratio of change in mean circulatory pressure to a change in blood volume, and took compliance to be the reciprocal of stiffness. Other investigators who also utilized this method were Harlan, Smith, and Richardson (1967) and Shoukas and Sagawa (1971). Some researchers (Echt, Johannes, Gauer, and Lange, 1974; Engelberg and DuBois, 1959) chose to infuse a given volume of fluid and observe pressure change. In another study, Shoukas and Sagawa (1973) altered the pressure by ligation and observed changes in volume. Rose and Freis (1957) and Ross, Frahm, and Braunwald (1961) altered pressure using drugs.
The studies have also differed in whether the organ was isolated and/or excised for the study or was kept in vivo. In some cases it was beneficial to isolate the structure from surrounding factors that would influence or cloud results. Still others found a theoretical model to be helpful in analyzing what was actually happening.

The species chosen to be studied was also an important factor in understanding results. For instance, although similarities exist in the arteries and veins of dogfish and man, Opdyke and Wilde (1975) found an atypical vascular volume distensibility curve in their study of dogfish that was attributed to a unique pore enlargement that takes place at a very low capillary pressure making initial vascular volume variable in dogfish. Primitive and higher vertebrates may exhibit a basic difference in capillary structure, making the application of results selective.

In the literature there appears to be only three studies of compliance in the placenta. In 1970, Power and Longo demonstrated that pressure-flow interactions exist in the fetal circulation of placentas in sheep and that they can be modified by maternal vascular pressures. In 1973, Bissonnette and Farrell studied pressure-flow and pressure-volume relationships in the fetal placental circulation and found the fetal placental vascular bed to be capable of distension. They suggested that aside from the recruitment of previously unperfused fetal vascular channels, fetal placental vascular volume is capable of approximately a 40 percent increase by distension. At the time the
present study was in progress, Power and Gilbert were studying umbilical vascular compliance in sheep and testing for possible interactions between maternal and fetal circulations.

**Conditions of the Mother Affecting the Placenta**

With the close communication between maternal and fetal circulations, it is not surprising that various conditions in the mother affect the placenta, and therefore the well-being of the fetus. In this section, the literature on the effects of labor on circulation and the fetus and the phenomenon of the supine hypotensive syndrome are reviewed. Because diabetes has been shown to have an effect on various tissues of the body in altering compliance, it has been included in the review of the literature. In the study, maternal pressures were varied and the resulting change in placental blood volume was observed. Therefore, a review of the literature dealing with hypertension, another factor that places the pregnant woman and her fetus at risk, is also reviewed.

**Labor**

Labor is generally considered to consist of three phases: the first, effacement and dilatation of the cervix; the second, expulsion of the fetus; and the third, expulsion of the placenta. Each stage has an effect on uterine circulation and this effect has been the object of much investigation over several decades.

Greiss (1966) pointed out that the study of the effect of labor on blood flow has been limited by methodology, inability to detect or
induce labor in lower species, and the inaccessibility of human subjects for such studies. The first direct observations were reported by Ahlquist and Woodbury in 1947 when they noted a reciprocal relationship between uterine blood flow and uterine contractions. In 1958, Assali, Dasgupta, Kolin, and Holms reported a significant decrease in blood flow proportional to the intensity and duration of the contraction. Later studies (Borell, Fernstrom, Ohlson, and Wiquist, 1964; Ramsey, Corner, and Donner, 1963) suggested that this reduced flow is partially due to a reduction in the diameter of the arteries supplying certain parts of the intervillous space rather than being due to external compression of the myometrium. Oxygenation in fetal placental and capillary blood decreased as a function of maternal placental blood flow (Guilbeau and Reneau, 1973; Longo, Hill, and Power, 1972; Reneau, Guilbeau, and Cameron, 1974).

Reactive hyperemia followed as the uterus relaxed between contractions, providing a protective mechanism to aid the fetus in withstanding the normally short periods of ischemia during labor. Frequency of contraction was also found to have a reciprocal correlation to blood flow in investigations by Greiss and Anderson (1968). In a previous report, Greiss (1966) had found that the degree of recovery following a contraction was dependent upon the duration of the resting phase of the cycle and that this "myometrial diastole" was very important in the maintenance of uterine blood flow. Hess and Hon (1960) reported that a decrease in the duration of diastole evoked by more frequent or more prolonged contractions caused fetal tachycardia or
bradycardia. If the contraction was of a tetanic nature and was not followed by relaxation, the subsequent uterine ischemia was so severe that the survival of the fetus was threatened.

Through the years differing views have been expressed as to what happens to the intervillous space volume during labor. Some thought that during a contraction, blood was squeezed out of the placenta like water being squeezed from a sponge, but as early as 1958, Hendricks reported that as the intervillous space pressure rose, the veins were occluded, preventing outflow and causing a resultant rise in intervillous space pressure as pressure in the amniotic cavity increased. Amniotic fluid pressure was found to rise from 15-60 mm Hg and fall to resting tonus again over a period of one minute for a contraction of moderate intensity according to Caldeyro-Barcia and Poseiro (1960). Ramsey and others (1963) demonstrated a maintenance of intervillous space volume during contractions in their experiments with rhesus monkeys. The findings of Borell and others (1964) in human subjects supported this view. The volume of the intervillous space did not fall to below 80 percent of its resting level due to the collapse of the maternal veins preventing outflow. Thus the oxygen needs of the fetus are provided for during a contraction.

Another group of investigators suspect an increasing volume rather than merely maintenance of intervillous space volume. Maternal venous outflow is halted at the beginning of a uterine contractions, pressing the content of the uterine mural veins into the maternal venous reservoir (Ramsey and others, 1963). The maternal arteries continue, however,
to carry blood into the intervillous space until a higher myometrical pressure is reached that can eventually halt inflow too (Borell and others, 1964; Ramsey and others, 1963). It may be that it is at this point when intrauterine pressure exceeds arterial blood pressure that a woman feels ischemic uterine pain. The delay in the halt of inflow results in an increased intervillous space volume during a contraction. Transverse isotonic scanning was used to study one laboring patient and demonstrated an increase in placental thickness (Smyth, 1973). Bleker, Kloosterman, Mieras, Oosting, and Salle (1975) examined six patients during labor with ultrasound and found an increase in the length, thickness, and surface of the placental area in periods of contraction compared to relaxation. They concluded that this makes more maternal blood available for exchange with the fetal compartment during a contraction.

During the second stage of labor, Greiss (1966) found that expulsive efforts by the mother in bearing down caused a marked decrease in uterine blood flow. He pointed out that it is good that these expulsive efforts are generally synchronized with uterine contractions because the full advantages of uterine relaxation can then be realized. As early as 1958, Assali and others reported that uterine blood flow falls slightly after delivery of the fetus and precipitously after expulsion of the placenta.

Supine Hypotensive Syndrome

The phenomenon of supine hypotensive syndrome has been studied by many investigators and appears in the literature under such terms as
physiologic shock, inferior vena caval syndrome, and syncope. The gravid uterus occludes the inferior vena cava reducing the pressure head and gradient in the vascular system which consequently reduces cardiac output and results in a drop in the maternal arterial blood pressure. It has been seen most commonly in late pregnancy when the pregnant woman lies in the supine position and may be seen earlier in the pregnancy in the presence of twins or hydramnios. The mother may experience pallor, numbness, diaphoresis, general discomfort, and even epigastric distress.

McRoberts first described what he termed "postural shock" in pregnancy in 1951. This awakened new interest in the upper and lower parts of the vena cava when the recumbent position was assumed. However, when the woman was on her side or in a semi-reclining position the venous pulse waves became synchronous and the uterine contractions became slower and more intense. Ullery, Vorys, and Handsek (1961) showed that cardiac output is 14 percent less when the patient is in the supine position as compared to cardiac output in the lateral position. Reid (1957) considered it to be more a form of syncope rather than shock.

Incidence of the syndrome was reported to be 11 percent by Howard (1953) and later, 6 percent by Wright (1962) when defined by a decrease of 30 mm Hg in systolic blood pressure or a systolic pressure of 80 mm Hg or less. Some investigators (Barclay, Renegar, and Nelson, 1968; Kerr and Scott, 1965) have pointed out that most women do not experience this syndrome because their vertebral collateral venous cir-
culation in the external and internal vertebral venous plexuses ensure adequate venous return to the heart. As early as 1954, Browne had suspected that some enhancing mechanism such as an A-V shunt existed to protect placental blood flow in the majority of patients.

Other investigators have reported the deleterious effects on the fetus when the mother experiences this phenomenon (Bieniarz, Sepulveda, and Caldeyro-Barcia, 1965). Reed, Teteris, and Essig (1970) reported a case study in which fetal bradycardia was documented with electrocardiography when the mother had a drop in blood pressure and rise in pulse in the supine position.

**Diabetes**

Pregnancy itself produces a diabetogenic effect in the nondiabetic pregnant woman. As the fetus draws glucose from the maternal system maternal hypoglycemia may result. Lactogen produced from the human placenta increases the mobilization of free fatty acids and diminishes the effect of maternal insulin. Estrogen, another hormone produced in increasing amounts during pregnancy, is thought to act as an insulin antagonist. Progesterone, a third hormone, may decrease the effect of insulin peripherally.

However, the pregnant diabetic is at higher risk than the pregnant nondiabetic. Schuler (1979) points out that she is at high risk to develop pre-eclampsia and has an increased incidence of unexplained stillbirths. North, Mazumdar, and Logrillo (1977) compared date from nondiabetic women in 1950-1969 and found that the death rate in infants
exceeded infants of nondiabetic mothers at all gestational ages and in every birth-weight-for-gestational-age category.

Some (Babson, 1975; O'Sullivan, Charles and Mahan, 1973) advocated that early recognition and control of hyperglycemia can avert increased perinatal mortality and put the well-controlled diabetic at the same risk level as nonpregnant diabetics. Others maintain that diabetes is far more complicated than simple glucose control and has widespread effects on various body tissues. Turner, Harris, Bloom, and Uren (1977) suggested that abnormalities of glucagon in diabetics are probably a secondary, rather than a primary, event.

Widespread elastin and collagen abnormalities that affect tissue biochemically, morphologically, and functionally are found to accompany diabetes mellitus (Caulfield, 1972; Hamlin and Kohn, 1972; Huston and Abboud, 1962; Pillsbury, Hung, Kyle, and Freis, 1974). Siperstein (1970) postulated that these connective tissue abnormalities are the primary defect of the disease. Schuyler and others (1976) reported from their study of young diabetics, a decreased elastic recoil at middle and low lung volumes along with decreased total lung capacity. They noted that the changes in the pressure-volume curve to the left observed in their study could be due to alterations of both collagen and elastin. Other investigators (Huston and Abboud, 1962; Pillsbury and other, 1974) found a decrease in arterial wall compliance in diabetic children possibly related to changes in the scleroprotein function in large elastic arteries. Williamson and Kilo (1977) in their review of the literature felt that there was general agreement that thickening
of the capillary basement membranes was the ultrastructural hallmark of diabetic angiography.

With such widespread changes as these, it would not be surprising if changes were also seen in the placenta. Aladjem (1967) found areas of syncytial detachment, rupture, or outright disappearance of the membrane. Emmrich, Fuchs, Heinke, Jutzi, and Goedl (1976) found the epithelial and endothelial basal laminae to be thinner in placentas from diabetic mothers when compared with controls. They found them to be particularly thin in the regions with syncytiovascular membranes. In another study (1975) they found increased fibrin deposits in the wall of the distal spiral artery and noted a thickening of the walls with narrowing of the lumen in the myometrial arteries.

As in other states of stress on the body, some compensatory mechanisms have been suspected in diabetic pregnant women. HbAIC is a normal minor hemoglobin having glucose linked high affinity for oxygen. A remarkable difference has been noted (Schwarz, H. C., Kings, K. C., Schwartz, A. L., Edmunds, D., and Schwartz, R., 1976) between the levels of this hormone in nonpregnant and pregnant diabetics, reflecting possibly a compensatory mechanism to protect the fetus by facilitating oxygen exchange between mother and fetus.

**Hypertension**

Most investigators believe that hypertension in the pregnant woman places her at a high risk for fetal loss and a great chance of developing superimposed toxemia. Toxemia refers to a specific hyper-
tensive disease of pregnancy in which there is edema, proteinuria, and blood pressure elevation in the pre-eclamptic state and the development of seizures and coma in the eclamptic state. The toxemias of pregnancy are responsible for the major maternal and perinatal mortalities (Sullivan, 1974).

Chronic nontoxemic hypertension has been associated with increased perinatal mortality rate, increased number of premature deliveries, and increased incidence of intrauterine growth retardation. The risk is directly related to the severity of the hypertension according to some investigators (Cibils, 1974; Tweedie and Mengert, 1965). The poor fetal outcome corresponds to decreased uteroplacental blood flow (Browne and Veal, 1953) which in turn is due to atherosclerosis and sclerosis of placental spiral arterioles (Brosens, 1964). Brinkman and others (1975) observed an increase in uteroplacental vascular resistance and reduction in uteroplacental blood flow following the induction of mild hypertension in their study of sheep. Arias (1975) found a reduced blood volume and low birth weight infants in hypertensive mothers and suggested that this is secondary to varying degrees of venous and arterial vasoconstriction.

Page and Christianson (1976) did a prospective study of 13,000 pregnant women during 1959-1967 and analyzed the impact of elevated blood pressure and/or proteinuria on the outcome of pregnancy. The mean arterial pressure and absolute levels of blood pressure prior to labor and delivery rather than the degree of rise of blood pressure was found to be significant. Significant proteinuria alone and especi-
ally with hypertension was also found to be detrimental to pregnancy outcome. They believed decreased uteroplacental blood flow to be the common denominator for the increase in stillbirth rate, perinatal mortality rate, the frequency of intrauterine growth retardation, and neonatal morbidity.

Early in the second trimester, an inadequate maternal vascular response to placentation heralds the complication of pre-eclampsia (Brosens and Renaer, 1972; Chakravorty, 1967) to retard fetal growth and produce low-birth-weight-for-gestational-age infants. Others (Baird, Thomson, and Billewicz, 1957; Beaudry and Sutherland, 1960; Butler, Alberman, and Goldstein, 1969) found no reduction in birth weight for infants with mothers having mild or moderate pre-eclamptic toxemia. DeSouza, John, and Richards (1976) did not find significant differences in the distribution of mean birth weight, head size, and placental weight between toxemic and nontoxemic mothers. They attributed this to present obstetric management which reduces the severity and duration of the illness.

In the early literature, Tenney and Parker (1936; 1940) described placentas of toxemic placentas as having increased aging and degeneration of syncytiotrophoblast. Abitboll, Driscoll, and Ober (1976) produced experimental toxemia in rabbits and found diffuse congestion, old and recent infarcts, and syncytial knots in the placentas resembling those found in human toxemia. Fibrin was deposited between trophoblastic cords, at the perimeter of zones of infarction, and even in the uninvolved placental tissue. Benirschke and Driscoll (1967) showed that
especially in toxemia in the human the compromised maternal circulation is the usual cause of placental infarction. Emmrich and others (1975) found that maternal hypertension produced a thickening of the arterial wall in myometrial, basal, and decidual arteries.

The etiology of toxemias of pregnancy remains a mystery having been linked to placental prostaglandin levels (Demers and Gabbe, 1976), placental ischemia (Page, 1972), prolactin response (Mati, Mugambi, Odipo, and Nguli, 1977), and lowered immune response (Jenkins, Need, and Rajah, 1977; Kitzmiller and Benirschke, 1973; Robertson, 1976).

**Update of the Literature from 1976-1978**

Research, like a living organism, continues to grow, and expands our current knowledge, giving new insights and raising more questions. This section is a brief review of the pertinent literature from 1976 through 1978 in a subject order paralleling the preceding review of the literature.

After 1976 nothing new was found reported in regards to structure of the normal placenta, but in 1977 Erian proposed a mathematical modeling of the maternal blood flow in the placenta which casts new light on function. In his model, the villous tree is represented as a continuous deformable porous solid in which permeability increases with increasing local flow speed. He suggested that fluid inertia gives jet penetration, thus promoting mass transport.

In 1978, Reynolds dealt with a portion of the maternal-fetal unit that there was little information on, the umbilical venous blood flow.
He described this as being like a pulsometer-type pump, and pointed out that it is unique among physiologic systems. The venous blood flows easily with little obstruction, under small but frequently applied pressure variations resulting from the pulsations in the two umbilical arteries coiling around it.

Venuto and others (1976) wanted to study the effect of arterial pressure on uterine blood flow. They chose to use rabbits because the placental implantation is like that of humans, and because unlike that of sheep, the rabbit uterus can synthesize renin like the human. When perfusion pressures ranged between 60 and 140 mm Hg, uteroplacental blood flow remained relatively constant. However, when ganglionic blockade reduced pressures to 36 through 42 mm Hg, uteroplacental blood flow fell sharply as expressed by percentage of cardiac output and absolute flow. They proposed that the relative constancy of blood flow was due to autoregulation of flow by an intrinsic myogenic property of the vasculature which alters resistance in response to pressure.

Two new articles dealing with the value of knowing compliance appeared in the literature. Grossman, Braunwald, Mann, McLaurin, and Green (1977) found that end systolic pressure-volume relations reflect the contractile state of the left ventricular myocardium and pointed out that quantitation of these relations may provide a new approach for assessment of myocardial function. Wisneski and Bristow (1978) went one step further from assessment to the arena of therapeutics and proposed that left ventricular stiffness can be changed by shifting
the pressure-volume curve such as is already seen in connection with coronary artery bypass graft surgery and the use of nitroprusside. They also reported that ischemia or hypoxia shifts the pressure-volume curve to the left, where a small change in volume can result in markedly elevated pressure.

The cause of the inferior vena caval syndrome was questioned by Abitbol (1978). Body position did not make a difference while compression of both renal veins or of the inferior vena cava above the renal veins produced only a moderate drop in blood pressure or flow and never caused shock and bradycardia. Collateral circulation appeared to be adequate when checked radiologically. He pointed out that this syndrome occurs primarily with the use of conductive anesthesia or other pharmacologic agents. Suonio, Simpanen, Olkkonen, and Haring (1976) observed that position did make a difference, though not statistically significant. The supine position lowered placental blood flow by 17 percent from that seen in the left lateral position. Although there were no significant differences in mean heart rates or mean systolic and diastolic blood pressures, two of the ten patients studied exhibited a marked decrease in systolic and diastolic blood pressures in the supine position and had a subjective feeling of fainting. One of these had a marked decrease in placental blood flow. Interestingly enough, the mean placental flow was significantly lower in the upright position compared to the left lateral recumbent position. One patient who was near to fainting showed a tremendous decrease in placental blood flow. Perhaps for some pregnant women there exists
"the upright syndrome" that may also have an unfavorable effect on the fetus, according to the investigators.

Feeling that studies of placentas from diabetic women had yielded inconsistent and contradictory results, Jones and Fox (1976) studied placentas from seven women known to be diabetic and on insulin therapy prior to the onset of pregnancy but without complicating pre-eclampsia. They noted patchy focal syncytiotrophoblastic necrosis, focal thickening of the villous trophoblastic membrane, and immature endothelial cells of the villous capillaries, but claimed that the placental function was probably not adversely affected. They were unable to demonstrate any correlation between severity of diabetes with severity of placental abnormalities.

Thliveris and Baskett (1978) studied the placentas in prolonged pregnancy and found moderate to severe necrosis in placental villi and fibrinoid deposition in varying degrees.

Concern for hypertension in pregnancy was quite evident in the recent literature. Friedman and Neff (1978) found that the combination of a diastolic blood pressure exceeding 84 mm Hg at any point during pregnancy, and maximum proteinuria were most closely correlated with the poorest perinatal outcome. Inadequate weight gain appeared to place the fetus or surviving infant in jeopardy. A surprising finding was that hypotension with diastole less than 65 mm Hg in the third trimester carried a threefold risk for fetal death and a higher risk of neonatal death. Some investigators might feel that this was linked to an inadequate uteroplacental perfusion. For instance, in Clavero-
Nunez' (1977) study of placental blood flow in 57 women near-term, those placentas with decreased blood flow were associated with fetal distress during labor and neonatal depression. Necropsy findings on three infants who died and neonatologists' diagnoses of six who were depressed for five minutes following birth, was attributed to hypoxia.

Cavanagh, Rao, Tsai, and O'Connor (1977) tested the concept that uteroplacental ischemia triggers toxemia. By partially occluding the uterine arteries, they were able to produce toxemia in baboons and found lesions in the kidney tissue like those seen in humans with toxemia. Naeye (1978) reported that chronic ischemia due to inadequate uteroplacental blood flow caused perinatal death and directly correlated with hypertension during pregnancy, proteinuria, and advancing maternal age. The organs of infants who died were growth retarded like the placenta, in a manner similar to that usually seen with late gestational undernutrition.

Soffronoff, Kaufmann, and Connaughton (1977) found extreme hypovolemia to be present in the case of severe hypertensive disease and uteroplacental insufficiency. High hematocrit values were found in pre-eclamptics by Naeye (1977) in his prospective study of over 30,000 pregnancies. This, along with damage to the walls of the uterine arteries by hypertension, appeared to predispose the toxemic patient to thrombi and fatal placental infarcts.

Similar to this fibrinoid deposition in the uterine arterial walls was the syncytial degeneration and fibrinoid deposition in placental villi from hypertensive women studied by Thliveris and Speroff.
(1977). The findings in their study of no increase in the cellular activity of secretory granules in the placenta challenges the idea that an increased placental secretion of renin causes hypertension in pregnancy. Rolschau (1977) questioned that infarctions and intervillous thromboses have the same pathogenesis. He found nothing to suggest that placentas with intervillous thromboses had been subjected to anoxia and proposed that infarcted placentas are possibly caused by stenosis of small decidual vessels or transitory local ischemia.

More challenges to all the evidences cited for lesions characteristic of pre-eclampsia were raised by Wynn (1977) who maintained that the changes were not sufficiently specific or consistent to permit diagnosis of pre-eclampsia in distinction from a normal pregnancy or some other hypertensive disorder.

Questions might be raised as to the usefulness of microscopic examination of the placenta, membranes, and cord, but Keenan, Steichen, Mahmood, and Altshuler (1977) found that the findings correlated with clinical outcome. They suggested that this could be important especially in the early diagnosis of neonatal sepsis which occurs more frequently when placental inflammation is present.

Summary

The placenta, a unique organ of maternal and fetal origin, has a varied structure among the species and during gestation, and performs complex functions vital to the growth and development of the fetus. Although a great deal of investigation has been done in regard to the
placenta as an organ of transfer little is known about placental com-
pliance which was the focus of this research.
Chapter 3

MATERNAL PLACENTAL VASCULAR COMPLIANCE IN RABBITS

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Introduction

The relationship between pressure change and volume change in the circulation is termed vascular compliance. It has been extensively studied in the entire body (Engelberg and DuBois, 1959; Rashkind, Lewis, Henderson, Heiman, and Dietrich, 1953; Richardson, Stallings, and Guyton, 1961; Shoukas and Sagawa, 1971; 1973), in isolated segments of the vascular system (Diana and Shadue, 1975; Opdyke and Wilde, 1975; Young, Cholvin, and Roth, 1975), and in the heart (Mirsky and Parmley, 1973; Romero, Covell, and Friedman, 1972) and lungs (Engelberg and DuBois, 1959; Shoukas, 1975). Some investigators have infused or withdrawn volume and studied the effect on pressure (Drees and Rothe, 1974), while others have changed pressure and noted the effect on volume (Shoukas, 1975).

The compliance of the placentas has not been reported previously, although it is of importance in the control of the placental circulation and in exchange of a variety of substances. The purpose of this study was to measure the compliance of the maternal placental circulation.
using radioactive markers to measure blood volume at different maternal pressures. Rabbits were selected for study because their hemochorial placental structure resembles that of primates. We have previously reported values for fetal compliance in the umbilical circulation and have given data to suggest an interaction between maternal and fetal circulations in the placenta (Power and Gilbert, 1977).

Method

The principle of the method was to measure placental blood volume using both erythrocyte and plasma markers, at different maternal pressures. Maternal arterial ($P_a$) and venous ($P_v$) pressures were used to estimate the intervillous space ($P_{IVS}$) pressure, the great preponderance of placental blood being assumed to lie in the intervillous lake. The intervillous space pressure may be estimated because the data of Reynolds, Freese, Bieniarz, Caldeyro-Barcia, Mendez-Bauer, and Escarcena (1968) in primates and Moll and Kunzel (1973) in rabbits describing the longitudinal pressure drop from uterine artery to small arterioles immediately proximal to the intervillous space suggest the intervillous space pressure parallels and is only a few millimeters Hg greater than uterine venous pressure.

A total of 27 pregnant New Zealand white rabbits were studied at fetal gestational ages ranging from 26 to 28 days. A 9 ml blood sample was withdrawn from an ear artery into a syringe containing 1 ml of ACD solution. This blood, 50 $\mu$Ci $^{51}$Cr, and 0.5 ml of 10 percent NaCl solution to prevent hemolysis were mixed and incubated for 20 minutes.
at 37°C. The mixture was then centrifuged and the plasma and buffy-coat layers removed. The erythrocytes were washed with isotonic saline and centrifuged twice to lower free $^{51}$Cr to less than 1 percent. Finally, 5µCi of $^{125}$I-labelled serum albumin, as a plasma marker, and enough isotonic saline to reconstitute the volume were added to the erythrocyte suspension and together comprised the mixture for injection.

We anesthetized the maternal rabbit with 15-20 mg/kg pentobarbital and gave additional barbiturate as needed. With the rabbit in a supine position, femoral arterial and venous catheters were inserted and advanced 3 cm into the iliac vessels for recording maternal blood pressure and obtaining blood samples. Both pressures were referenced to mid-chest level. We opened the abdomen with a midline incision and placed adjustable ties loosely around the inferior vena cava and the decending aorta. By adjusting the tension of these ties, the arterial and venous blood pressures in uterine vessels could be varied. Then we looped braided ties around four segments of the uterus each containing a fetus and its placenta. Care was taken to avoid impairment of the circulation or excessive handling of the uterus.

We administered the radioactive blood mixture through the venous catheter and allowed 10 minutes mixing time. Then maternal arterial or venous pressure was set to some predetermined level by adjusting one of the ties. After the pressures had been stable for 15 seconds at the desired levels, the snare around one fetus and its placenta was pulled tight, trapping the blood present in the placenta. In each maternal rabbit, four fetuses were snared: one at normal pressures, one with
the inferior vena cava (IVC) occluded, one with the aorta fully occluded, and one with the aorta partially occluded (to provide an arterial pressure midway between normal and full aortic occlusion). The order in which we varied maternal pressure was randomized. Maternal blood was sampled prior to each snaring.

Placentas were removed in a manner designed to minimize loss or redistribution of blood between surrounding myometrium and placental tissue. The fetus was delivered through an incision in the uterine wall and the cord was cut. The uterus was invaginated and a second snare was looped over the placenta and drawn tight at the junction of its basal plate and surrounding uterine wall. The myometrium lying outside the snare and fetal membranes were trimmed away, leaving only the basal plate, its ensnared blood volume, and a nubbin of myometrium at the point of attachment.

We placed 1 ml samples of maternal blood and entire placentas in separate counting vials which were weighed before and after filling. A gamma well counter (Nuclear-Chicago Corp., model 1085) counted each vial for three periods of four minutes each. Hematocrits of maternal blood were determined in capillary tubes in duplicate, and averaged and corrected for trapped plasma by multiplying by 0.96.

In two rabbits, we carried out the above procedure with the exception that maternal pressure was not changed before snaring the fetuses. All volume data were normalized to 1 g of placental weight. In calculating the $^{51}$Cr activity per ml of erythrocytes, appropriate cor-
rections were made for background, hematocrit ratio, and the Compton effect from the $^{51}$Cr.

Placental weight was determined by weighing the placenta and subtracting the weight of plasma and erythrocytes.

Results

Five rabbits, either in active labor or with fetuses in only one uterine horn, were excluded from the study on the basis of the different dynamics in the utering-placental circulation which may have been present. The data from the remaining 20 rabbits were summarized in Table 1. When the inferior vena cava was occluded, venous pressure rose on an average 6.7 mm Hg. Placental blood volume also rose 63 percent higher than the volume at control maternal blood pressure ($P > 0.001$). When the aorta was partially occluded, causing the arterial pressure to fall and the venous pressure to tend to rise slightly, the net effect was a small rise in placental blood volume. When the aorta was fully occluded, placental blood volume was not altered significantly even though arterial pressure fell to a very low level. The venous pressure, however, did not change appreciable.

To be able to relate placental blood volume to a single placental pressure, we calculated intervillous space pressure ($P_{IVS}$) from maternal arterial and venous pressures on the assumption of a venous-to-total resistance ratio ($R_v/R_T$) if 0.02, estimated from the data of Moll and Kunzel (1973). Using this ratio, we plotted the pressure-volume relationship in the placenta as shown in Figure 1. The compli-
ance, calculated from the slope of the curve, was 0.0471 (±0.0005 SE) ml/mm Hg/g. The figure also shows how the pressure-volume relationship would change for differing resistance ratios.

Hematocrit of the maternal blood in the placenta at normal maternal blood pressure averaged 27 percent, appreciably less than the circulating hematocrit of 38 percent. The maternal placental hematocrit was thus 0.71 of the circulating hematocrit. When the inferior vena cava was occluded, placental hematocrit rose 29 percent higher than placental hematocrit at normal maternal pressure. When the aorta was occluded, there was little change. These results are shown in Figure 2.

In the two control rabbits in which the maternal pressure was not altered, we found no systematic change in volume. The average blood volume was 0.434 ml/g placental tissue (SE±0.052 ml/g).

Discussion

The results of the study are summarized in Table 1. They indicate that changes in maternal placental blood volume tend to parallel changes in maternal venous pressure and are little influenced by arterial pressure. Since most placental blood lies in the intervillous space, it seems likely that intervillous space pressure would be similar to venous pressure. In fact, Moll and Kunzel (1973) found the pressure in small arterioles immediately proximal to the intervillous space to average only 8 mm Hg when arterial pressure averaged 101 mm Hg. In our rabbits, arterial pressure was 72 mm Hg, and therefore the pressure in pre-intervillous space vessels is likely to have been somewhat less
than 8 mm Hg. Since the venous pressure in our rabbits averaged 5.5 mm Hg, the pressure drop from pre-intervillous space vessels to the inferior vena cava must have been in the range of 2-3 mm Hg. Using Moll and Kunzel's results for intervillous space pressure which indicate that intervillous space channels and uterine veins are a low-resistance segment of the placental circulation, and our values for arterial and venous pressures, we estimate that veins account for only about 2 percent of the total placental resistance in these experiments, i.e., \( R_V/R_T = 0.02 \). Using this ratio, intervillous space pressure was calculated and plotted against blood volume for different pressure conditions (Figure 1). The correlation was high \( (r = 0.999) \). We calculated compliance from the slope of the relationship and found it to be \( 0.0471 \ (\pm 0.0005 \ SE) \) ml/mm Hg/g.

We also calculated placental compliance assuming different resistance ratios, attempting to get some estimate of the error involved in assuming a resistance ratio of 0.02. In one instance, we assumed \( R_V/R_T = 0 \); i.e., we ignored arterial pressure entirely, and plotted blood volume against venous pressure (Figure 1). We found placental compliance to be \( 0.0468 \ (\pm 0.0056 \ SE) \) ml/mm Hg/g with a correlation coefficient of 0.973. Secondly, we assumed \( R_V/R_T = 0.04 \), an upper limit based on data of Moll and Kunzel (1973). Using this ratio, calculated compliance was \( 0.0455 \ (\pm 0.0045 \ SE) \) ml/mm Hg/g with \( r = 0.981 \). These values are not greatly different from the compliance calculated from a ratio of 0.02, indicating that negligible error
(less than 4 percent) is introduced in assuming an resistance ratio in the range from 0 to 0.04.

Another possible source of error in the compliance determination might be introduced if the resistance ratio were to change when either the aorta or inferior vena cava was occluded. We reasoned that if the ratio did change with aorta or inferior vena cava occlusion, it would be reduced in either case. That is, when the inferior vena cava were occluded, venous pressure would rise and possibly distend the veins, whereas the arteries would remain the same size or possibly decrease in diameter due to the fall in aortic pressure that accompanied the inferior vena cava occlusion. Under these circumstances, the resistance ratio should, if anything, be less than when aortic and inferior vena cava pressures are normal. When the aorta was occluded, the resultant fall in aortic pressure might result in a decrease in diameter of the arteries and again cause the resistance ratio to decrease. Taking the extreme case, where \( \frac{R_V}{R_T} = 0.02 \) at normal aortic and inferior vena cava pressures, but approached 0 when either the aorta or inferior vena cava were occluded, we plotted the pressure-volume relationship and obtained a compliance value of 0.0512 (±0.0013 SE) ml/mm/Hg/g. This compares with the value of 0.0471 ml/mm Hg/g assuming the resistance ratio remained at 0.02 at control pressures and when the aorta and inferior vena cava were occluded. Thus, an error of less than 9 percent would be introduced if the resistances were to change with aorta or inferior vena caval occlusion.
It might be argued that blood volume measurements were appreciably in error because of redistribution between the placenta and myometrium after snaring. This error is not likely to be large for at least two reasons. One is that, compared on a per-gram-of-tissue basis, the volume of blood contained in the placenta is severalfold larger than in the myometrium. Second, the method of snaring left only about 1 g of myometrium surrounding a typical 8-g placenta. Taken together, these indicate only a small vascular space, outside the intervillous space, would be available for redistribution.

To answer this question definitively, it would have been desirable to measure the static vascular pressure in the placenta after snaring. We could have then compared this pressure to the intervillous space pressure which we calculated assuming a constant resistance ratio. From this we could have determined if a redistribution of blood had occurred due to equilibration of pressures. This proved to be technically very difficult. When we inserted 26-guage needles under stereoscopic control into several snared placentas to measure the static pressure, we obtained only variable, unstable reading which were highly dependent upon needle placement. Because of these difficulties, we elected to use calculated values for intervillous space pressure.

The hematocrit of maternal blood in the placenta has not been reported previously. Like the hematocrit in such organs as the lungs (Rapaport, Kuida, Haynes, and Dexter, 1956) and kidneys (Pappenheimer and Kinter, 1956), as well as the fetal blood in the umbilical circulation (Newcomb and Power, 1975), the hematocrit of maternal blood in
the placenta is lower than the circulating hematocrit. This may be due to plasma skimming or, as proposed by Fung (1973), because erythrocytes are directed preferentially into faster flowing streams. The rise in hematocrit when the intervillous space is occluded so that it more closely approximates circulating hematocrit may be due to increased blood vessel diameter and slower flow and hence, less preferential erythrocyte distribution and plasma skimming. The low placental hematocrit indicates that erythrocytes pass through the placenta faster than plasma, a finding that may have implications as far as gas exchange is concerned.

In the study, when the inferior vena cava was occluded we observed a situation that possibly parallels supine hypotensive syndrome, in which the gravid near-term uterus occludes the inferior vena cava when a woman lies in the supine position. This reduces the pressure head and gradient in the vascular system and diminishes uteroplacental blood flow, which Reed, Teteris, and Essig (1970) suggest causes fetal hypoxia and resultant distress. This change in maternal hemodynamics may also affect the fetal circulation because of an interaction in the placenta. When the maternal inferior vena cava is occluded and venous pressure rises, intervillous space pressure also rises. Volume accumulates, the extent to which being determined by maternal placental vascular compliance, placental membranes and connective tissue are stretched, and fetal blood tends to be displaced out of the exchange area (Power and Gilbert, 1977).
Then change in intervillous space pressure during labor is complicated. One one hand, the amniotic fluid pressure rises as the uterus contracts, tending to squeeze blood out of the intervillous space. On the other hand, the contracting myometrium tends to collapse the veins draining the placenta and raise the intervillous space pressure. The net result of these changes determines the effective transmural intervillous space pressure during a contraction. When these pressures can be measured, they could be used together with the compliance reported here in Figure 1, to predict intervillous space volume changes during labor.

Overall, our results suggest that maternal placental volume would be maintained during transient hypotension and would increase when venous pressure is elevated.

Acknowledgments

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Table 1

Plasma, Erythrocyte, and Total Blood Volumes and Hematocrits of the Intervillous Space at Different Maternal Pressures

<table>
<thead>
<tr>
<th></th>
<th>$P_{\text{arterial}}$ (mmHg)</th>
<th>$P_{\text{venous}}$ (mmHg)</th>
<th>Hct IVS</th>
<th>Vol$_{\text{plasma}}$ (ml/g)</th>
<th>Vol$_{\text{RBC}}$ (ml/gm)</th>
<th>Vol$_{\text{Total}}$ (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>71.8</td>
<td>3.5**</td>
<td>5.5</td>
<td>.267</td>
<td>.336</td>
<td>.120</td>
</tr>
<tr>
<td>IVC Clamped</td>
<td>45.5</td>
<td>3.8*</td>
<td>12.2</td>
<td>.354</td>
<td>.508</td>
<td>.221</td>
</tr>
<tr>
<td>Aorta partially occluded</td>
<td>33.8</td>
<td>2.3*</td>
<td>7.0</td>
<td>.269</td>
<td>.334</td>
<td>.133</td>
</tr>
<tr>
<td>Aorta fully occluded</td>
<td>13.5</td>
<td>1.8*</td>
<td>5.4</td>
<td>.270</td>
<td>.286</td>
<td>.103</td>
</tr>
</tbody>
</table>

* significantly different from control. p 0.001
** mean one standard error
Effect of Changing Maternal Intervillous Space Pressure on Placental Blood Volume

Intervillous space pressure was calculated assuming venous to total resistance ratios from 0 to 0.04. Compliance was calculated from the slope of each curve.
Figure 2

Hematocrits of Maternal Circulating Blood and Maternal Placental Blood at Different Pressures in the Intervillous Space
Chapter 4

SUMMARY, CONCLUSIONS, IMPLICATIONS, AND RECOMMENDATIONS

The last chapter of this study contains: (1) a grief summary of the preceding three chapters, (2) conclusions of the study and their implications, and, (3) recommendations for future research that arise from the study.

Summary

The first three chapters dealt with an analysis of problem, a review of the related literature, and the study itself. A brief summary of them follows.

Chapter 1

In the first chapter it was pointed out that a clearer understanding of the physiology and pathophysiology of the placenta would be the first step in providing better care to mother and baby. Although much investigation has been made into the morphology of the placenta, the blood flow in the uterus and placenta, and the exchange functions of the placenta, there has been limited study into the focus of this study, compliance, which could affect the volume of maternal blood in contact with placental fetal villi.

The purpose of the study, which was conducted using a true experimental design, was to determine the compliance of the maternal
component of the uteroplacental unit in rabbits. Erythrocytes and plasma were labeled with radioactive isotopes for the purpose of measuring the volume of maternal blood in the placenta at different maternal pressures.

Limitations of the study included: the difficulty in generalizing the results of the study on rabbit placentas directly to inferences for human placentas, the inability of taking into account the effect of the placenta's changing shape on its compliance, the use of anesthetized animals with the unknown alteration of distribution of blood flow, and the lack of knowledge of the actual ratio of arterial to venous resistance in the uteroplacental unit of the rabbit.

Terms specific to the study were defined and an overview of the remainder of the thesis given.

Chapter 2

The review of the literature in the second chapter covered three major areas and raised questions pertinent to the study.

The placenta is a unique organ composed almost entirely of vascular elements of maternal and fetal origin, and functions as the fetal lung, intestines, and kidney. It varies greatly in structure between species and even during gestation in some animals, making classification somewhat difficult.

Compliance was the second major area of focus. The pressure-volume relationships in various body systems and organs have been studied using a variety of methods. Physiologic factors as well
as disease have been recognized to alter these relationships, and in turn, the function of the organ or system. Compliance has been studied in the fetal placental circulation and the umbilical circulation, but has not been determined for the maternal placental circulation.

Various conditions in the mother that affect the placenta and thus the fetus were next considered. The onset of labor brings about dramatic changes in uterine blood flow and pressures in the amniotic cavity and intervillous space. The volume of blood in the intervillous space has been studied with some investigators reporting a preservation of volume and other reporting an increased volume to ensure adequate oxygenation of the fetus.

The phenomenon of supine hypotensive syndrome occurs in a minority of pregnancies due to the pressure of the gravid uterus on the inferior vena cava and inadequate collateral venous circulation, according to most investigators. More recently some have questioned whether it is rather due to present anesthesia practices. The present study gave some insight into what happens to the volume of blood in the intervillous space when the blood return through the inferior vena cava was diminished.

It has long been realized that the pregnant woman with diabetes or hypertension carries an infant at high risk. Diabetes exhibits widespread effects throughout the body in various organs and tissues, including the placenta. Compliance has been noted to be reduced in the lungs and arterial walls, but has not been studied in the placenta.
Maternal hypertension has been noted to produce changes in arterial walls, and toxemia has been seen to affect the ultrastructure of the placenta. Again, the effect on the compliance of the placenta has not been investigated.

Chapter 3

The article reporting the body of this research which was submitted to and published in the American Journal of Physiology, comprised the third chapter.

In it the details of the method and procedures for data collection and calculations were described. The volume of maternal blood in the placentas was plotted against the estimated intervillous space pressure, and compliance was calculated from the slope of the curve.

The results of the study were reported and indicated that changes in maternal placental blood volume tend to parallel changes in maternal venous pressure and are little influenced by arterial pressure. Possible sources of error were pointed out and discussed.

A sidelight of the study was the reporting of the hematocrit of maternal blood in the placenta to be lower than the circulating hematocrit.

Conclusions and Implications

Over the intervillous space pressure range from normal to high, placental compliance was found to be 0.0471 ml/mm Hg/g placental tissue. In comparison to the intrathoracic compliance of 1.2 ml/mm Hg/kg
body weight in humans (Shapiro, Harrison, and Trout, 1975) and the liver compliance of 32.9 to 40.7 ml/mm Hg/kg liver weight in fetal sheep (Gentsler, Gilbert, and Power, 1979), this would show the placenta to be a very compliant organ under normal conditions. This would be favorable to fetal well-being as a significant addition of blood volume would not make intervillous space pressure rise greatly, with the possibility of clamping down the fetal placental villi and inhibiting exchange.

The results suggest that placental maternal blood volume would be maintained during transient hypotension which would also be a factor in favor of the fetus. When venous pressure was elevated, the placental maternal blood volume increased which appears would enhance maternal fetal exchange. However, this was only a transient increase and does not indicate what would happen when elevated pressure was more long-standing. The study would support recent findings that under normal circumstances, even when the venous return to the heart is blocked via the inferior vena cava, maternal blood volume in the placenta is maintained.

The lower hematocrit of maternal blood within the placenta indicates that erythrocytes transit the placenta faster than plasma, possibly to allow for more rapid and efficient exchange as the blood bathes the fetal placental villi.

The implications for nursing were more general than would be the case if the study was more clinically centered. In the clinical setting, nurses are involved with meeting patients' educational and
psychological needs in coping with their condition. Pregnancy, for most women, is fraught with concern for the well-being of the baby, and how it can be given the best start in life. The results of the study can in a small way, reassure the mother-to-be that normally her body tends to do what is best in providing for the needs of the fetus under a variety of circumstances.

In the educational setting nurses are made aware that their practics is, or should be, based on principle. An understanding of anatomy and physiology provides a rationale for therapy. But present knowledge is the fruit of past research. Participation in primary research, such as the present study, gives nursing an appreciation for the vast amount of effort on the part of many disciplines that contribute to improvement of nursing education and patient care.

**Recommendations for Further Research**

In basic research, a study such as this provides but a small piece of a very large puzzle. The significance of the results may appear small, but they provide building blocks for future studies in the large work of increasing our understanding of the body and its functions.

Some recommendations for further research that arise from the study are suggested:

1. Repeat this study with a fifth fetus being snared at a pressure midway between the normal pressure and the high pressure obtained by clamping the inferior vena cava completely.
2. Repeat this study, measuring the compliance of placentas in rabbits with induced hypertension and compare that compliance with what was found in this study of placentas in normotensive rabbits.

3. Conduct a study of the compliance of the maternal component of the uteroplacental unit in sheep using volume infusion rather than pressure change.

4. Conduct a study in which the collagenous and elastic elements in placentas of diabetic patients are compared to the collagenous and elastic elements in placentas of nondiabetic patients.

5. Conduct a study in which the compliance of placentas from hypertensive patients is compared to that of placentas from normotensive patients.
REFERENCES


Gentsler, C. C., Gilbert, R. D., and Power, G. G. Compliance of the structural elements in the fetal sheep liver. Loma Linda, Loma Linda University, School of Medicine, 1979. (Unpublished)


