EXERCISE IN PREGNANCY

an experimental study of maternal and fetal responses to exercise in sheep

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Cover: Gabriëlle Huig

To the memory of Hester

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Introduction

Pregnant women in the western world usually reduce their physical activity as term approaches. However, in recent years increasing numbers of women also voluntarily engage in relatively strenuous exercise during pregnancy. Both pregnancy and physical activity increase the body's metabolic demands, but the physiologic adaptations to these combined demands are only partially understood. On the one hand, one would expect adverse maternal or fetal effects because of the seemingly conflicting demands of the acutely exercising muscles and of the pregnant uterus. On the other hand, however, nature presents several examples in which strenuous physical activity during pregnancy co-exists with a favorable outcome of pregnancy. Therefore, further investigation of the adaptations to exercise in pregnant individuals is important from the viewpoint of physiology as well as of obstetrics.

The study of the physiologic effects of exercise during pregnancy is complicated for several reasons. These include 1) large baseline changes within each individual during the course of gestation, 2) wide variation in baseline values between individuals (e.g., physical condition), 3) many differences in exercise load and/or experimental design between studies, 4) wide normal variation in fetal outcome, 5) possible interference of fear and other "stresses", 6) relative inaccessability of the fetus, 7) ethical and legal problems relative to studies in humans, and 8) profound species differences. Many aspects of fetal physiology can only be investigated with the use of invasive techniques. Obviously their use must be restricted to animal studies and, consequently, relatively little is known of the human fetus per se. Although one has to be careful in extrapolating animal data to man, animal studies provide a powerful tool in improving our understanding of human physiology.

This thesis represents an effort to obtain a better understanding of the physiologic adaptations to the combined stresses of exercise and pregnancy. It consists of four chapters. Chapter one extensively reviews the literature, discussing the physiologic changes which occur both in pregnancy and exercise, as well as the adaptations to these combined stresses. Rather than to focus on the differences in experimental design and species we emphasize the common denominator in what is known and not known about the subject, and point out fertile topics for further investigation. Chapters two and three present the results of our experimental studies of acute maternal and fetal responses to exercise in chronically instrumented sheep. Finally, chapter four deals with the main physiologic changes during exercise in pregnancy.

CHAPTER ONE

Maternal and fetal responses to exercise during pregnancy

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1. Introduction

The one objective of all living organisms is the preservation of a constant environment (33). For those tissues with higher than normal metabolic demands, such as working muscles and the pregnant uterus, this requires an increased supply of oxygen and nutrients. Mammals will deplete their energy stores in the metabolic process unless they can replete these by increasing their food uptake. Meeting the demands is essential for survival of the individual, for its success in procreation, and ultimately for the success of the species.

Muscles represent a tissue mass in which energy requirements increase acutely and drastically with exercise. Some of the energy is derived from the oxygen and nutrients stored within the tissues and some is derived anaerobically. However, the sustained energy output of exercising muscles is limited by the substrate supply to the tissues. Local metabolic factors probably regulate this availability by increasing the blood flow to the exercising muscles, a process that is enhanced by physical training.

The pregnant uterus and its contents represents a growing mass of tissue, which needs a relatively constant supply of substrates. Its metabolic demands gradually increase as gestation advances, and insufficient supply will result in stunted growth or fetal death. Local metabolic factors, mediated by the production of hormones, probably result in a dilated uterine vascular bed. This contributes to the other cardiovascular effects of pregnancy such as increased blood volume and increased cardiac output, and in these respects pregnancy resembles physical training.

Although there are similarities between the physiologic adaptations to pregnancy and to chronic exercise, the metabolic demands of acutely exercising muscles would seem to conflict with those requirements of the pregnant uterus. Nature

presents several ways in which the increased energy demands of physical activity and pregnancy are met. Some species, such as Cetacea (whales) and Ursidae (bears), store large amounts of body fat before pregnancy and/or early in gestation, utilizing it during the latter part of pregnancy. However, almost all species actively gather food throughout pregnancy. Most herbivores display a more or less normal activity pattern throughout pregnancy and are subject to predation. Although some of them may protect themselves by their strength, many rely on their speed and/or endurance to successfully outrun a predator. In several species pregnant individuals also participate in extended migrations which require considerable energy expenditure. Generally, this physical activity does not result in fetal loss. Carnivores themselves are often subject to predation and depend upon their speed, strength, and agility for food gathering. Therefore it is not surprising that, for example, the big cats are quite active throughout pregnancy.

Pregnant women in the western world usually reduce their physical activity towards term. However this is not possible for many women, especially those in the developing countries. In these women pregnancy outcome is less favorable, but it would be an oversimplification to blame this on their physical activities alone. Overall, the combination of exercise during pregnancy demonstrates the remarkable reserve of physiological adjustments.

In the following review we will explore what is known and what is not known of the physiological adjustments when the stress of exercise is superimposed upon that of pregnancy. Among the questions which we will consider are the following: 1) To what extent do the maternal metabolic, endocrinologic, respiratory, and circulatory responses to heavy physical activity differ from those in nonpregnant individuals? 2) How should one best normalize calculations of various physiological functions in pregnant women? 3) How should exercise be quantified during pregnancy? 4) To what extent is working capacity affected by pregnancy? 5) To what extent does temperature increase during exercise, and what is its significance for mother and fetus? 6) To what degree does exercise affect uterine blood flow and the transport of respiratory gases and substrates across the placenta? 7) What metabolic, respiratory, and circulatory adjustments take place in the fetus during maternal exercise? 8) What are the long-term sequalae on pregnancy outcome?

2. *Maternal responses*

A fundamental question concerns the extent to which responses to exercise during pregnancy differ from those of the nonpregnant state. This problem can only be investigated in carefully controlled studies against a background of knowledge of the physiologic changes of both pregnancy and exercise. Clearly it is beyond the scope of this review to discuss critically the literature on either of these topics. In each section we will briefly summarize the relevant information about the physiologic adaptations to pregnancy and those responses to acute exercise and physical training. For the pregnant individual the increase in body weight, girth and

other dimensions, and body composition, as well as the presence of the growing fetus(es) affect the baseline values of many physiologic variables relevant to the study of exercise. The response to exercise also is affected by differences in subjects (e.g. species, sex, age, body weight, physical condition, motivation), in body position, and in exercise regimen (type, level, time course).

A further question of importance concerns how best to measure exercise stress of the subject under study. Quantification is essential for a correct interpretation of the response, however the total amount of external work can only be accurately expressed in absolute terms (Joules) with bicycle or handcrank ergometers. It is more difficult, or impossible, to assess accurately the external work during treadmill or steptest exercise, or during activities such as swimming and skiing.

The different types of exercise are often classified as weightbearing (e.g., treadmill, steptest) and nonweightbearing (e.g., bicycling, swimming). Although the importance of separating these two forms of exercise during pregnancy is obvious, differences in body position, dimensions, and composition during pregnancy may affect the mechanical efficiency during either type of exercise. Thus, a given amount of work may not present the same physiologic burden to different study subjects. For example, the amount of energy required to pedal a bicycle ergometer will be higher for someone with edematous legs than for a normal subject. By expressing exercise level as a percentage of maximal O_2 consumption (% $\dot{V}O_2$ max) one minimizes the variability caused by such factors as species, sex, age, physical condition, various diseases, and motivation.

Expressing the work level in these terms is generally accepted as the most accurate and universal measure of exercise stress. However, in pregnant subjects only two studies have reported exercise in terms of % $\dot{V}O_2$max (219, 220, 333). Some other studies during pregnancy have used the heart rate increase as an index of the workload. Although normally heart rate varies almost linearly with O_2 consumption at submaximal exercise levels, this relation is affected by a variety of factors. The assumption that it is uninfluenced by pregnancy has not been validated. Most other studies of exercise during pregnancy have expressed the work level only in terms of treadmill speed, inclination, et cetera.

Because of the many variables which affect the responses to pregnancy and exercise few, if any, studies on the combined subject can be considered well controlled. Although the physiologic adaptations to exercise during pregnancy can be expected to be most pronounced during exhaustive exercise near-term, only a limited number of studies have been performed under such extreme conditions. Therefore in many instances it is impossible for one to determine to what extent exercise responses differ as a result of pregnancy per se.

2.1 Oxygen consumption

At rest all energy is generated by oxidative degradation of nutrients (14). Resting O_2 consumption ($\dot{V}O_2$) is influenced by several factors including species, body size

and composition, sex, age (14, 57, 190), position (106), and environmental factors (e.g. temperature). Measured under standard conditions in the nonpregnant adult, the energy used exclusively for the maintenance of vegetative functions and heat production is referred to as basal metabolic rate. During pregnancy nutrients are also used for maternal weight increase, and the growth, metabolism, and muscular activity of the fetus. Strictly speaking one cannot measure O_2 consumption, or basal metabolic rate, of the mother alone.

During pregnancy resting O_2 consumption increases with advancing gestational age to a maximum near term (18, 226, 279, 322, 332). In humans this value is 16 to 32% above that of nonpregnant controls (82, 193, 205, 206, 208, 266, 322, 332), while in near-term pygmy goats it is increased 21% (93). Theoretically the higher resting $\dot{V}O_2$ during pregnancy results from increased tissue mass, higher metabolic rate per gram of tissue, and/or more work for vital functions. In humans the pregnancy weight increase equals about 10 kg, consisting of fetus = 3.5, placenta + membranes = 0.5, amniotic fluid = 1, uterus = 1.2, blood = 1.6, breast = 1, interstitial fluid = 1.2. The metabolic rate of these different components varies from relatively high values in the fetus and placenta to zero for the amniotic fluid. Maternal O_2 consumption is only 4% higher than that of the nonpregnant state after subtracting for the total uterine contents (71). Thus, the metabolic rate of the other maternal tissues appears to be virtually unaffected by pregnancy, and although cardiac and respiratory work are probably increased slightly, the largest increase results from the products of gestation.

During constant load exercise in nonpregnant individuals, O_2 consumption rapidly increases to reach a quasi steady state within 3 minutes (14), and then continues to increase slightly with time (141). Oxygen consumption increases pari passu with the exercise level (14), until at $\dot{V}O_2$ max the subject reaches exhaustion within about 10 minutes (200). Recovery is characterized by both a rapid and a slow component to the $\dot{V}O_2$ fall, the rapid component being a function of exercise intensity and lactate metabolism, while the slow component seems more dependent on the Q_{10} effect of temperature on metabolism (142).

Because oxygen consumption increases with both exercise level and gestational age, exercise during pregnancy produces the most pronounced increases in O_2 consumption near term at the highest exercise levels (18, 101, 102, 139, 266, 279, 322, 332). During late pregnancy submaximal exercise is associated with about 10% higher absolute values for O_2 consumption than during the nonpregnant state. This phenomenon has been observed during weightbearing exercise in humans (193) and goats (93), as well as during handcrank and bicycle exercise in humans (30, 100, 106, 139, 193, 205, 206, 266, 322). Although two authors reported lower O_2 consumption values in exercising gravidas as compared with nonpregnant women (30, 101, 102), the control subjects probably were not well matched.

During pregnancy the amount of oxygen required for exercise, represented by the increase in O_2 consumption, has been reported to be higher during treadmill (93, 193, 318), handcrank (160), and bicycle exercise (205, 206, 266, 322) than in controls (Table 1). In contrast, other workers found the increase in O_2 consumption with

Table 1. Oxygen consumption during bicycle exercise in the sitting position.

Author, year	Subjects	Oxygen Consumption					
		Rest		Exercise		Exercise-Rest	
		Absolute ($ml.min^{-1}$)	P-NP (%)	Absolute ($ml.min^{-1}$)	P-NP (%)	Absolute ($ml.min^{-1}$)	P-NP (%)
Ueland et al, 1973	P	330	17	836	15	506	13
	NP	281		728		447	
Knuttgen and Emerson, 1974	P	249	30	1060	3	811	–3
	NP	191		1030		839	
Pernoll et al, 1975	P	331	33	1167	15	836	8
	NP	248		1019		771	
Lehmann and Regnat, 1976	P	340	16	1265	11	925	9
	NP	293		1141		848	
Edwards et al, 1981	P	243	27	883	4	640	–2
	NP	191		847		656	

P, Pregnant; NP, Nonpregnant.

exercise to be similar in pregnant women and controls (100, 193) (Table 1). These latter studies are supported by other reports that the caloric cost of exercise is slightly, but not significantly higher during pregnancy (see below). The added weight of pregnancy will result in a lower efficiency (task/energy expenditure) during treadmill exercise, but this is less evident on a bicycle. In addition, pregnancy-associated increased leg weight or a less efficient body position on the bicycle may demand a slightly higher total energy output to perform a given task, however, the amount of extra work cannot be accurately assessed. An increased energy requirement also could result from a reduced efficiency of the muscle cells, but this possibility has not been studied during pregnancy. Any inefficiency will reduce working capacity unless it is compensated for by an increased maximal ability to take up oxygen and to expend energy.

An individual's exercise capability can be judged from the highest oxygen uptake ($\dot{V}O_2$ max) he can achieve (75). Although the physiological implications and criteria for measuring $\dot{V}O_2$ max have been reviewed by several authors (10, 14, 75, 157, 200, 283), little is known about $\dot{V}O_2$ max during pregnancy. Maximal O_2 consumption can only be reached when a sufficiently large (>50% of total) muscle mass is involved in the activity, such as in running up a grade (283). Thus, during arm exercise the highest $\dot{V}O_2$ attainable ($\dot{V}O_2$ peak) is about 70% of $\dot{V}O_2$ max, while during bicycle exercise it approaches 90% of $\dot{V}O_2$ max. In the supine position $\dot{V}O_2$ peak equals only about 85% of that obtained while sitting (14). Maximal O_2 consumption can objectively be measured and is minimally affected by poor motivation, day to day variation, ambient and body temperatures, and a variety of stresses including acute blood loss, dehydration (283), and previous exercise (313). $\dot{V}O_2$ max is lower in women than in men, decreases with age, and varies over a wide range among different individuals (189, 283).

Maximal O_2 consumption during pregnancy has not been studied in great detail. Lotgering et al (219) observed a 5.6 fold increase in O_2 consumption to 32 $l.min^{-1}.kg^{-1}$ during maximal exercise in pregnant ewes, but it is unknown whether or not this is higher than in nonpregnant sheep. If one could extrapolate from the above observations at submaximal work levels in humans, a given maximal task during pregnancy would require about a 10% higher absolute $\dot{V}O_2$ max. Wilson and Gisolfi (333) found an insignificant 7% increase in $\dot{V}O_2$ max in pregnant rats. Whether or not a similar increase in maximal O_2 consumption during normal pregnancy is also present in other species has not been examined. Physical training of a sedentary nonpregnant individual can increase $\dot{V}O_2$ max up to 33% (283). Because during pregnancy every task requires a higher O_2 consumption than in the nonpregnant state, some training effect seems inevitable unless a more sedentary lifestyle is adopted. The elevated blood volume and its resulting greater O_2 carrying capacity are also likely to increase $\dot{V}O_2$ max (14). Thus it seems that $\dot{V}O_2$ max should increase during pregnancy, or that the organism is at least capable of doing so, but this needs to be confirmed experimentally. Several investigators have attempted to assess the $\dot{V}O_2$ max of pregnant women by extrapolation from the heart rate at submaximal workloads (96, 109-113, 271). This will be discussed in the section on physical working capacity.

Although physical training does not affect resting O_2 consumption, it markedly increases $\dot{V}O_2$ max up to 33% in sedentary men (289). However, in individuals with relatively high initial $\dot{V}O_2$ max values training does not produce such pronounced results (189). A case report showed that O_2 consumption during submaximal treadmill exercise increased linearly with the pregnancy weight increase, when fairly strenuous daily exercise was maintained during pregnancy (287). In addition, the O_2 consumption prior to and following treadmill exercise in mildly trained women was found not significantly different from that in untrained pregnant women (303). This suggests that the work efficiency is not altered significantly by physical training during pregnancy, but does not provide direct information as to an effect on $\dot{V}O_2$ max.

Little is known of the effects of training on $\dot{V}O_2$ max during pregnancy. Wilson and Gisolfi (333) found a nonsignificant 13% increase in $\dot{V}O_2$ max in rats undergoing training during pregnancy. In those animals which had been trained prior to as well as during pregnancy $\dot{V}O_2$ max was 23% higher than in sedentary pregnant rats, but the increase during pregnancy per se was 8%, as in the control group. The extent to which $\dot{V}O_2$ max during pregnancy is affected by training has not been studied in any other species. Neither has the question of whether the $\dot{V}O_2$ max increase of training can be further enhanced by pregnancy been explored. Bedrest reduces $\dot{V}O_2$ max as much as 28% in nonpregnant adults (289), and immobilization will presumably also lower this value during pregnancy. In severe cardiac or pulmonary disease $\dot{V}O_2$ max is sometimes markedly reduced, but whether or not pregnancy affects $\dot{V}O_2$ max under these circumstances has not been explored. It is obvious that further studies are needed to obtain a more complete picture of this important physiologic indicator of physical condition.

The O_2 consumption of an individual is the sum of the O_2 consumptions of the various tissues. Because the metabolic rate of muscle, brain, and other tissues is much higher than that of tissues such as bone and adipose tissue (190), O_2 consumption reflects body composition as well as body size. In order to normalize for body size between different species and individuals one can express O_2 consumption per unit weight (kg), assuming a similar body composition. However, it is difficult to quantify, or to normalize for, differences in body composition, and no agreement exists (14, 57, 190) as to which correction is best, particularly during pregnancy.

The multifactorial cause of the increased O_2 consumption during pregnancy raises the question of how to normalize for these changes in a physiologically meaningful way. Figure 1 shows several ways in which this can be calculated. As is evident, during pregnancy O_2 consumption in absolute terms ($ml.min^{-1}$) is 20% higher at rest but only 10% higher with exercise, as compared with nonpregnant controls. When calculated per unit surface area ($ml.min^{-1}.m^{-2}$) $\dot{V}O_2$ increases 11% at rest and only 2% during exercise. Calculated per unit weight ($ml.min^{-1}.kg^{-1}$) it changes insignificantly at both rest and with exercise, 3 and -6% respectively. Finally, when calculated per unit lean body mass ($ml.min^{-1}.kg^{-1}$) it does not change at rest and decreases 8% during exercise.

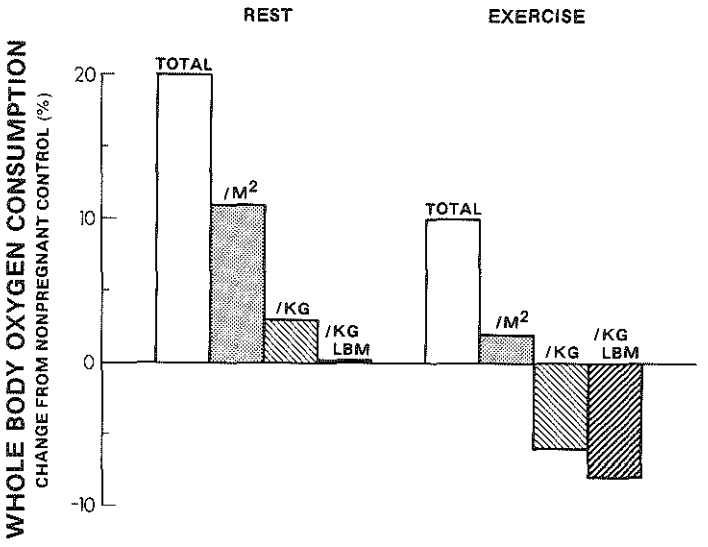

Figure 1. The effect of changes in body composition during pregnancy on the O_2 consumption at rest and during exercise, calculated in absolute terms ($ml.min^{-1}$), per square meter surface area, per kilogram body weight, and per kilogram lean body mass. We assumed the following increases during pregnancy: body weight 17% (to 70 from 60 kg), surface area 8% (to 1.80 from 1.67 m^2), fat free mass 20% (to 48 from 40 kg), resting $\dot{V}O_2$ 20% (to 360 from 300 $ml.min^{-1}$), exercise $\dot{V}O_2$ 10% (to 1980 from 1800 $ml.min^{-1}$).

Seitchik (299) reported that during quiet sitting O_2 consumption was unaffected by pregnancy if normalized for lean body mass, but Flanagan et al (122) observed an 8% increase. Although lean body mass does not completely reflect the changes in body composition during pregnancy, it appears to be the best approximation.

In nonpregnant individuals $\dot{V}O_2$ max normalized for body weight is considered to be the best indicator for the physical capacity to perform exercise (238). However, whether or not this is also true during pregnancy deserves further investigation. The increase in O_2 consumption during exercise results mainly from the increased work of the exercising muscles per se and those which alter body position, as well as the heart and respiratory muscles. The Q_{10} effect of temperature increases O_2 consumption in other tissues as well, but this increase is relatively small. Because muscle mass can be considered proportional to lean body mass, it is physiologically appropriate to normalize the exercise induced O_2 consumption increase for lean body mass in comparisons between species and individuals. During pregnancy however, muscle mass increases negligibly despite a marked increase in lean body mass. Thus, by normalizing for lean body mass during pregnancy the exercise induced $\dot{V}O_2$ increase will be falsely low. Whereas during pregnancy at rest O_2 consumption is related to lean body mass, during exercise the increase is more closely related to the lean body mass prior to pregnancy. The exercise induced changes in O_2 consumption are quantitatively more important than the pregnancy induced changes at rest. Therefore $\dot{V}O_2$ max during pregnancy is probably more closely related to the lean body mass prior to pregnancy. Nonetheless, it is not possible to normalize for pregnancy and exercise changes in a simple yet accurate manner.

2.2 Physical working capacity

Physical working capacity is the highest external work output reached under a specific set of circumstances. The term physical fitness is sometimes used as a synonym for physical working capacity, (or for $\dot{V}O_2$ max), but as it is so commonly used for the subjective expression of physical well being we will not use it. Physical working capacity is affected by $\dot{V}O_2$ peak, which in turn is affected by $\dot{V}O_2$ max as well as by a variety of conditions including somatic factors (sex, age, body dimensions, health), psychic factors (attitude, motivation), environmental factors (altitude, gas pressures, temperature, noise, air pollution), work characteristics (intensity, duration, rhythm, technique, position), training and adaptation (14, 283).

An increase in $\dot{V}O_2$ max during pregnancy (which seems likely – see above) will increase working capacity. However, this may be offset by motivation and general health as well as by a lower efficiency caused by changes in body dimensions and work position. To what extent a possible increase in $\dot{V}O_2$ max can compensate for a lower efficiency is unknown. Brühl et al (58) reported that fatigue was reached sooner in exercising pregnant rabbits than in controls. However, the number of animals and information about the controls were not reported. Erkkola (109)

observed that maximal fatigue was reached slightly sooner in pregnant women during a voluntary maximal bicycle test than in controls, but inadequate motivation during pregnancy may have affected these results.

By relating workload to the $\dot{V}O_2$ max or heart rate one reduces this subjective element. Several authors (86, 87, 126, 290, 308) estimated the physical working capacity, expressed as the absolute bicycle workload which elicits a heart rate of 170 bpm (PWC_{170}), by linear extrapolation from heart rate measurements at lower workloads. In three studies PWC_{170} was found unchanged during pregnancy (86, 87, 126), but two other studies indicated it was decreased by 12% (290, 308). With use of the Astrand index (15), (also an extrapolation from heart rate measurements at submaximal workloads), Erkkola (109) reported values comparable to those of the nonpregnant population, suggesting that working capacity is not significantly affected by pregnancy. However, inherent in these methods are the assumptions that maximal heart rate and the relation between heart rate and oxygen consumption do not change as the result of pregnancy. These assumptions need experimental verification. Training during pregnancy resulted in an 18% increase in $\dot{V}O_2$ max as predicted by heart rate (77). Training also resulted in about 10% higher work output during a voluntary maximal test near-term than in untrained controls (110). This may have resulted from a true increase in $\dot{V}O_2$ max or improved motivation in the trained women. Pathological conditions such as moderate anemia (276) and toxemia (308) have been reported not to affect PWC_{170}. However, situations in which $\dot{V}O_2$ max is reduced, such as prolonged bedrest or cardiac and pulmonary disease, inevitably result in a lowered working capacity.

The question as to whether or not physical working capacity is affected by pregnancy is important for both obstetrical and economic reasons. Furthermore, it is important to know whether an increase in $\dot{V}O_2$ max can compensate completely for the reduced efficiency (task/energy expenditure) during pregnancy. Because the study of physical working capacity is complicated by such uncontrollable factors as attitude and motivation, $\dot{V}O_2$ max probably is the most important objective indicator that needs further study.

2.3 Energy expenditure

As noted above, strictly speaking one cannot measure basal energy expenditure (metabolic rate) during pregnancy. At rest energy is generated by aerobic processes and the metabolic rate is therefore directly related to O_2 consumption, the relative amounts of substrates used for combustion, and the caloric equivalent of these nutrients (190). The caloric equivalent has little quantitative importance as it varies by only 6%, from 4.7 (fat) to 5.0 (carbohydrate) kcal.l O_2^{-1}. The contribution of proteins to metabolism can be calculated from the urinary nitrogen excretion, but is often ignored as it represents a relatively small (<7%) and constant error (14). The nonprotein respiratory quotient (RQ) reflects the relative amounts of fat (RQ = 0.7) and carbohydrate (RQ = 1.0). Depending upon the diet RQ at rest varies from 0.75 to 0.95, equaling about 0.85 on a normal diet in nonpregnant adults (70). Knuttgen

(193) reported a higher resting RQ in near term pregnant women (0.83) than 6 weeks postpartum (0.76), but other investigators (38, 264) have not confirmed this observation. Consequently, during pregnancy the increases in metabolic rate and $\dot{V}O_2$ are similar (38, 39, 147, 205, 206, 299), and can largely be attributed to the changes in total (38) or lean body mass (299).

During aerobic exercise the metabolic rate is also determined by $\dot{V}O_2$ and the substrates used for combustion (10). With subjects on a normal diet RQ increases with the intensity of shortterm exercise (70), reflecting a higher percentage of energy delivered by carbohydrates. With more prolonged exercise the RQ decreases gradually as the glycogen stores are depleted and more energy is derived from fat (70). For subjects on a carbohydrate diet the absolute value of RQ during prolonged exercise remains elevated above the value of individuals on other diets. In addition, because of greater glycogen stores, they have a higher working capacity than subjects on a normal or high fat diet (70).

The term "anaerobic threshold" has been used to express the exercise level above which the lactate concentration in exercising muscles increases, and equals about 50% $\dot{V}O_2$ max in untrained persons (13). Above this level the blood lactate concentration increases with the work load, but it is a poor indicator of the degree of anaerobic metabolism and cannot provide quantitative information (14). Although some lactic acid is removed during exercise per se, most is eliminated during the recovery period. During recovery the fast component of the recovery $\dot{V}O_2$ is used mainly for the repletion of body O_2 stores and of high energy bonds ("alactacid O_2 debt"), while the slow component is used for lactic acid removal. The processes used in lactate removal, glycogen resynthesis and oxidation to CO_2 and H_2O, require about twice the amount of O_2 as that required for aerobic metabolism (14). This increases the RQ during and especially following exercise, and affects the calculation of the metabolic rate from $\dot{V}O_2$ and RQ.

The respiratory quotient during (30, 38, 193, 264) and following exercise (332) is not significantly higher in pregnant women than in nonpregnant controls performing a similar task. Thus, it appears that the ratio of fat to carbohydrate used for combustion remains constant, and that the metabolic rate varies linearly with oxygen consumption.

The calculated metabolic costs of nonweightbearing exercise are slightly, but not significantly, higher during pregnancy (38, 297, 299). This agrees with some of the previously discussed studies on O_2 consumption (100, 193) and suggests that the efficiency to perform a given nonweightbearing task is unaffected by pregnancy. However, we do not have a satisfactory explanation for the higher O_2 consumption in other reports (205, 206, 266, 322) (Table 1). Fijalkowski et al (118, 119) noted that the metabolic cost of exercise during pregnancy is reduced 50%. The authors suggested that this resulted from a reduction in physical activity following delivery, but it seems more likely that methodological errors accounted for the large discrepancy. Most probably the differences in efficiency between pregnant and nonpregnant women are small in comparison to the errors involved in the methods. Further studies under more strenuous circumstances will be necessary to clarify the

extent to which O_2 consumption, respiratory quotient, and energy expenditure during exercise are affected by pregnancy.

In conclusion, there is little evidence for any significant difference in energy requirements for similar nonweightbearing submaximal exercise between pregnant and nonpregnant women. It is conceivable that differences occur at higher workloads, and this requires further study.

2.4 Metabolism

The balance of carbohydrates and fats used for combustion is not significantly affected by pregnancy, as discussed above. Nonetheless, the changes in plasma concentrations and the relative contribution of the different substrates to metabolism warrants further exploration. Although plasma concentrations of the different fuels reflect the balance between production (absorption and gluconeogenesis) and utilization, turnover rates are more important from a quantitative point of view (173). Metabolism during pregnancy has been studied chiefly in humans and sheep. Whereas monogastric animals absorb mainly hexoses and long chain fatty acids, ruminants absorb largely fermentation products such as acetate, propionate, butyrate, and lactate, so that the glucose needs in sheep must be met by gluconeogenesis (19).

Resting maternal glucose concentrations are slightly lower than in controls in humans (187, 192, 205, 206), guinea pigs (310), rats (128), and sheep with twin gestation (28), but are not significantly different in sheep with singleton pregnancy (314), and in horses (114). The glucose concentration falls linearly with advancing gestational age in man (192) and guineapigs (310). Although the glucose turnover rate increases in absolute terms, it remains constant when normalized for body weight in humans (187), guinea pigs (128), sheep (28), and horses (114).

The relative contribution of fats and carbohydrates to the energy expenditure of exercise depends not only upon the dietary intake, but also on the nature of the work (intensity, duration, rhythm), the state of physical training, and the state of health (14). The muscle glycogen level is related to the carbohydrate content of the diet (31). With exercise muscle glycogen content decreases with the workload (158), but exhaustion probably results from decreased hepatic glucose output and hypoglycemia (70). The blood glucose concentration decreases with the level and duration of exercise in fed humans (274), but increases in fasting man (49, 116), in sheep (53, 186), and in dogs and humans run to exhaustion (49).

In pregnant women undergoing moderate short-term exercise, plasma glucose concentrations decrease more than in nonpregnant controls and the decrease is slightly more pronounced at higher workloads (205, 206). However, with more prolonged exercise glucose levels tend to return to control values (196). Following exercise the glucose concentrations in pregnant women have been reported to increase (196), decrease (27, 205, 206), or remain constant (9). Studies in pregnant sheep showed that glucose concentrations increase with the level (68, 220) and duration of exercise (220), and only partially return to normal within 20 min after

exhaustive exercise (220). Whether this response differs quantitatively from that in nonpregnant sheep is not known.

Studies in nonpregnant man (337), dogs (174), and sheep (53, 186) show that moderate exercise increases the rates of gluconeogenesis and glucose turnover, with glucose oxidation providing about 20% of the total energy requirements. However, whether glucose turnover rate changes similarly during exercise in pregnant individuals has not been examined.

Following a meal resting lactate and pyruvate concentrations in pregnant women do not differ from nonpregnant controls (205, 206). However, the lactate concentration is increased up to 40% as is the lactate to pyruvate ratio in postabsorbative gravid rats (128) and in pregnant women in which the absorptive state was unspecified (27, 196). In the absence of studies on lactate utilization the physiological importance of these observations remains unclear.

Blood lactate concentration increases with the level of exercise. At moderate exercise levels its release from the muscle cells is approximately linear with work intensity, reaching a plateau at higher exercise levels (184). This results in increasing lactate concentrations in the exercising muscles which adversely influences the mobilization of free fatty acids and the working capacity (14). According to Hermansen and Vaage (159) 75% of the excess lactate is used for glycogen resynthesis during the recovery period. However, Brooks and Gaesser (54) suggest that less than 20% is used for glycogen resynthesis, that most lactate is oxidized, and that significant amounts are incorporated into amino acid and protein pools. The exercise induced increase in blood lactate concentration is proportionally larger than the increase in pyruvate, resulting in an increased lactate to pyruvate ratio which rapidly returns to normal following exercise (185). Higher lactate concentrations in pregnant women occur during (205, 206) and following (27, 196, 205, 206) moderate handcrank or bicycle exercise, although elevations were not observed in one study (322) during exercise of short duration and low intensity. In sheep, lactate concentrations increase with both the level (68, 73, 220) and duration of exercise (220), with incomplete recovery at 20 min following prolonged exercise at 70% $\dot{V}O_2$ max (220). Pyruvate concentrations increase only slightly during (205, 206) and following exercise in both pregnant and nonpregnant women (27, 205, 206). Consequently the lactate to pyruvate ratio increases more in pregnant women than in controls during (205, 206) and following exercise (27, 205, 206). In sheep the pyruvate increase was also smaller than that of lactate, with an insignificant increase in lactate to pyruvate ratio (73, 220). Whether this response differs from that in nonpregnant sheep is unknown.

During exercise the free fatty acid concentration and turnover rate (34), and their contribution to the energy expenditure increases with exercise duration (171), until at elevated lactate levels the free fatty acids turnover rate is reduced (172). Berg et al (27) observed a slight decrease in the free fatty acid concentration during exercise in both pregnant and nonpregnant women, but it is unknown whether the turnover rate during exercise in pregnancy differs from that in the nonpregnant state. In sheep acetate metabolism accounts for 20% of the total energy expenditure at rest

(7), but is unaffected (and is therefore quantitatively less important) by exercise (177, 186). In addition, acetate concentrations do not change during exercise in pregnant sheep (68). The contribution of protein metabolism to the energy expenditure of exercise is small (<7%) (14) and has not been studied during pregnancy.

Little information is available on the effects of physical training on metabolism. In horses training increases the glucose utilization by 50%, but does not affect resting plasma glucose concentrations (114). In trained humans plasma lactate levels are lower than in controls at every level of O_2 consumption (14), but it is unknown to what extent lactate is utilized differently. By reducing lactate production, training increases the utilization of free fatty acids (172). The importance of electrolytes, trace elements, and vitamins in exercise and training are only partially understood but deficiencies, especially of potassium (165), may affect performance (148). In vitro studies suggest that physical training during pregnancy does not markedly alter the intestinal transport of amino acids (97), but the effect of training on the metabolism of other substrates has not been studied during pregnancy.

2.5 Endocrinology

The hormonal regulation of metabolic homeostasis in pregnancy has been reviewed by Yen (336). The blood glucose concentration is largely maintained by the insulin to glucagon ratio and its effects on liver, fat, and muscle. During pregnancy the fasting insulin concentration is much higher whereas the glucagon concentration is not significantly different, so that the insulin to glucagon ratio is markedly increased. However, because of a pregnancy associated increase in peripheral insulin resistance, the marked hyperinsulinemia results in only a small decrease in plasma glucose concentration.

During exercise the increase in plasma glucose concentration is accompanied by an increase in glucagon in both man (49, 116) and sheep (53), whereas the insulin concentration is unchanged in these species (49, 53), or only slightly decreased in sheep during strenuous exercise (52). This suggests that the insulin to glucagon ratio is important at rest as well as during exercise, with glucagon the major regulator during exercise. The glucagon secretion during exercise may be stimulated by increased levels of circulating catecholamines concentrations (175), and thus vary with the work load. Somatostatin does not appear to affect the insulin to glucagon ratio during exercise, because exogenous somatostatin not only prevents the glucagon increase, but simultaneously reduces the insulin concentration (53).

In pregnant women Artal et al (9) observed a transient increase in glucagon and catecholamine concentrations immediately following exercise with a return to control values within 15 min, whereas the insulin concentration did not change significantly. The study did not include measurements during the exercise period and, as it was uncontrolled, it is unknown whether the changes differ from those in nonpregnant women.

Because of the multifactorial regulation of metabolism and hormone secretion, both at rest and during exercise, it is essential that studies of these facets of exercise during pregnancy include well matched controls. With the increase in resting insulin concentration during pregnancy and the development of insulin resistance one would anticipate a modified exercise response. However, presently it is impossible to conclude whether or not the exercise metabolism during pregnancy differs from the nonpregnant state. It is also unknown to what extent the alterations in maternal metabolism and endocrine function affect these functions in the fetus (see below). Further exploration of pregnancy exercise metabolism and endocrinology may not only increase our understanding of the basic physiologic mechanisms, but also our understanding of pregnancy complications such as diabetes mellitus. It is conceivable that repetitive exercise could be a tool in the clinical management of this disease, but that has not been studied.

2.6 Body temperature

Despite changes in ambient temperature, the body temperature of homeothermic organisms is maintained at a relatively constant level by precise balance of heat production and heat loss (14, 57). In addition to voluntary muscular activity, heat production can be increased by shivering and nonshivering thermogenesis. Heat loss to the environment is the result of conduction, convection, radiation, and evaporation. The anterior hypothalamus and the pre-optic region are sensitive to changes in the local core temperature, whereas the posterior hypothalamus receives information from skin receptors (14).

Immediately following ovulation "basal" body temperature rises approximately 0.5°C, in association with increased progesterone concentrations. During pregnancy this temperature increase persists until about midgestation, declining thereafter to normal levels (168). Although progesterone concentrations increase markedly towards term (320), the decline in basal body temperature has been attributed to the opposing effect of increased estrogen concentrations (168).

Pregnancy is associated with an increased rate of metabolism and therefore heat production. As discussed above this results chiefly from the growing maternal and fetoplacental mass, although other factors including the Q_{10} effect and increased cardiorespiratory work may also contribute.

The effect of pregnancy on thermal loss has, to our knowledge, not been studied. On one hand, the increased body weight will result in a relatively smaller surface area for heat dissipation. On the other hand, however, vasodilation will increase nonevaporative heat loss, while hyperventilation and increased sweat production will increase evaporative heat loss. Nonetheless, at present it seems most likely that the temperature changes during pregnancy are regulated by the central thermoregulatory mechanisms, modulated by the progesterone to estrogen ratio.

During exercise only 20 to 25% of the added energy expenditure is used for external work, the remaining 75 to 80% being transformed into heat, increasing total heat production by as much as 20 times resting values (10). Most of this heat is

lost to the environment but some is stored, primarily in the exercising muscles. As exercise proceeds the body temperature gradually increases until a "plateau" is reached, the level of which depends mainly upon the exercise intensity and to a lesser extent its duration (14). Following the termination of exercise temperature initially decreases rapidly, then more gradually returns to normal over a period of an hour or so (249).

Figure 2 depicts maternal body temperature at several levels and durations of exercise in near term pregnant ewes (after Lotgering et al [220]). Compared with humans, basal body temperature in sheep is approximately 2°C higher and heat loss across the skin is much lower. Within the first minutes of exercise maternal body temperature increased rapidly, the rate of increase varying with the exercise level (Fig. 2). After the initial rapid rise it gradually increased further. In these studies a plateau was not observed during even relatively prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. At exhaustion, reached either by short-term maximal exercise or by prolonged exercise at 70% $\dot{V}O_2$ max, the ewe's body temperature averaged 40.7°C (Fig. 2). Following exercise termination maternal temperature initially declined sharply, then gradually returned to normal. The recovery time varied with the

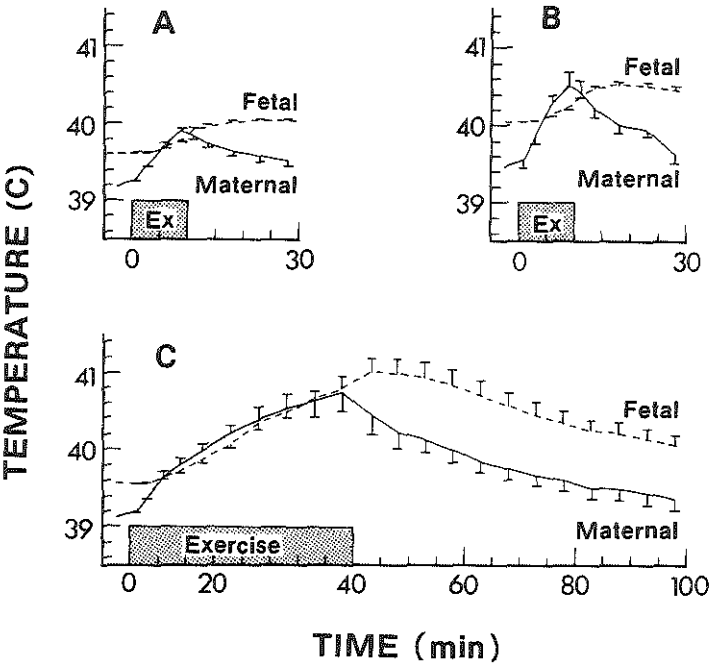

Figure 2. Maternal and fetal temperature changes in response to three different exercise regimens (after Lotgering et al [220]). A. 10 min exercise at 70% $\dot{V}O_2$ max, B. 10 min exercise at 100% $\dot{V}O_2$ max, C. 40 min exercise at 70% $\dot{V}O_2$ max.

exercise intensity and duration, so that even one hour after 40 min of exercise at 70% $\dot{V}O_2$ max, recovery was not complete. However, nonpregnant controls were not included in this study, thus it is unknown whether the response differs from that in the nonpregnant state. Finally, it should be noted that the mechanisms of heat loss in sheep differ from those in humans. These animals employ panting to a greater extent than humans, in which sweating is a more important mechanism.

To what extent the temperature increase during exercise affects the metabolic rate of tissues not actively working (Q_{10} effect) is uncertain. Physical training appears to enhance sweat production, resulting in increased capability of the organism to dissipate heat and a higher working capacity (14). Also, blood volume is elevated permitting greater cutaneous perfusion at a given thermal load, thus augmenting heat transfer from the core to the skin. The effect of training during pregnancy on body temperature control has not been studied. Because of the higher resting body temperature in early pregnancy, and the hormonal changes throughout gestation, it is conceivable that temperature regulation differs during exercise in pregnancy. This may affect working capacity and requires further study.

An additional consideration is that of exercise in a hot environment. This can result in excess hyperthermia, particularly in conjunction with relative dehydration or a high ambient humidity, due to inability to increase evaporative heat loss. In the human, dehydration with accompanying hypovolemia may cause a decrease in cutaneous blood flow in an attempt to maintain adequate cardiac filling, thus decreasing evaporative heat loss. These responses tend to reduce heat dissipation at a given thermal load.

2.7 Respiration and blood gases

The pregnancy associated changes in resting respiratory function have been the subject of several reviews (46, 168, 251, 330). Pregnancy is associated with hyperventilation due to increased progesterone levels, but the exact mode of action is unknown. Lung volumes are affected in the second half of pregnancy when the enlarging uterus elevates the diaphragm.

The changes in lung volumes during pregnancy and exercise are summarized in Figure 3. During the last trimester residual volume, expiratory reserve volume, functional residual capacity, and total lung capacity at rest decrease, while inspiratory capacity and inspiratory reserve volume increase. As a result vital capacity remains constant and tidal volume increases slightly. Because the breathing frequency remains constant or increases only slightly, the increase in respiratory minute ventilation results chiefly from the increase in tidal volume.

The exercise associated respiratory changes have been summarized by Asmussen (10). Minute ventilation increases as a function of exercise level, by an increase in both tidal volume and respiratory frequency. The changes are immediate and a steady state is reached within a few minutes after the onset of exercise of moderate intensity, while a gradual further increase is seen with heavy exercise. At very high levels of exercise the respiratory minute volume increases even further to compensate for the metabolic acidosis (329).

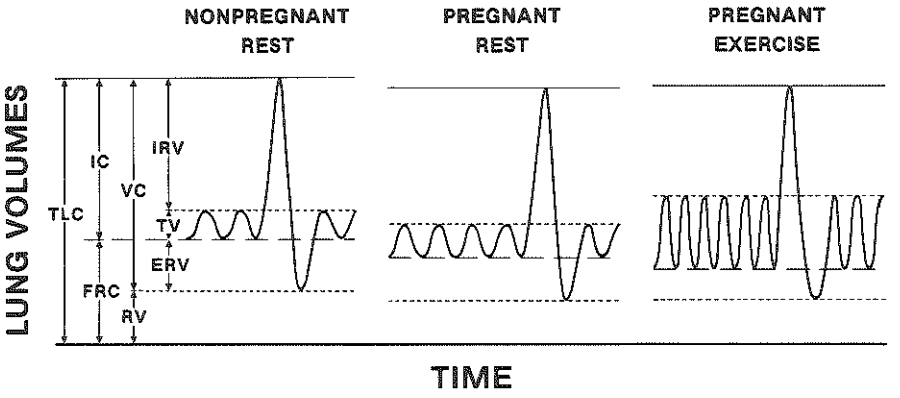

Figure 3. Changes in lung volumes during pregnancy (modified after Novy and Edwards [251]) and exercise. TLC = Total lung capacity, IC = Inspiratory capacity, FRC = Functional residual capacity, VC = Vital capacity, RV = Residual volume, ERV = Expiratory reserve volume, TV = Tidal volume.

In pregnant women tidal and respiratory minute volumes are increased above control values at rest as well as during and following exercise (82, 100-102, 139, 147, 193, 205, 206, 264, 332). These values increase with advancing gestational age, being about 30% higher near term (264, 332). A pregnant woman's respiratory frequency during and following either weightbearing or bicycle exercise is slightly, but not significantly, higher than in controls at comparable exercise levels (82, 86, 87, 101, 102, 139, 169, 170, 193, 205, 206, 264, 276, 332). With increasing exercise intensity tidal volume increases more than respiratory frequency, thus being progressively more responsible for the increase in respiratory minute volume (101, 102, 139, 205, 206, 332). Respiratory frequency returns to pre-exercise levels within 10 minutes following moderate short-term bicycle exercise in pregnant women as well as in controls (86, 87, 169, 170). However, in pregnant sheep it does not return to normal within 30 minutes following moderate prolonged treadmill exercise during which the respiratory frequency increased almost 200% (to 200 from 70 breaths per minute at rest) (107). Although this difference may have partially resulted from a higher workload, more likely it resulted mainly from the species difference, as hyperventilation is important for heat dissipation in sheep. Whether or not the response differed from that in nonpregnant sheep is unknown because nonpregnant controls were not included in the study. Other respiratory dynamics have not been studied in pregnant laboratory animals.

During pregnancy respiratory minute volume ($\dot{V}E$), increases to a greater extent) than O_2 consumption, as indicated by the higher ventilatory equivalent ($\dot{V}E/\dot{V}O_2$), both at rest and during exercise (100, 193, 264). Knuttgen and Emerson (100) observed a slight increase in ventilatory equivalent in pregnant women during treadmill and bicycle exercise, whereas others (100, 264) observed a slight decrease at a less strenuous workload. In both studies the changes were similar in pregnant and postpartum women and the difference between them may reflect the relative hyperventilation with increasing workload (10).

Because total pulmonary resistance during pregnancy is approximately one half of that observed in nonpregnant women (125), the excess work of breathing is probably small. The pulmonary diffusing capacity for CO ($D_{L_{CO}}$) at rest does not change markedly during pregnancy (23), but both alveolar ventilation and physiologic dead space increase by about 30% (264). During exercise the efficiency of gas exchange in nonpregnant individuals increases due to increased pulmonary diffusing capacity (23, 140), and alveolar ventilation (10), as well as more uniform distribution of ventilation and perfusion (92). The changes in pulmonary diffusing capacity (23) and alveolar ventilation (264) in exercising pregnant women are similar to those in nonpregnant controls. Thus, both at rest and during exercise hyperventilation constitutes the main respiratory difference between pregnant and nonpregnant individuals.

As a result of hyperventilation with increased alveolar ventilation at rest, during pregnancy the arterial CO_2 tension decreases from about 44 Torr to 32 Torr, the bicarbonate concentration decreases, the pH increases slightly, but the O_2 tension does not change (46). With exercise induced hyperventilation the arterial O_2 tension increases and the CO_2 tension decreases; pH increases initially, but progressively decreases as lactate accumulates during more heavy and prolonged exercise (10). In addition, the oxyhemoglobin dissociation curve shifts to the right as the result of the increased 2,3-DPG concentration, the temperature increase (179), and increases in several other factors including ATP and sodium concentration (191). This shift may be reduced or enhanced by the Bohr effect depending upon the level and the duration of exercise.

In the only controlled study of the changes in maternal respiratory gases during exercise, Lehmann (205, 206) found lower arterial CO_2 tensions in pregnant women than in controls both at rest and during exercise, reflecting the hyperventilation. The change in CO_2 tension during exercise in pregnant subjects was slightly smaller (2.5 Torr) than in the controls (6 Torr), whereas the change in pH and base deficit were slightly larger. Although the differences in exercise response between pregnant and nonpregnant women were probably not significant, they may have reflected the greater increase in lactate concentration as well as the reduced bicarbonate buffering during pregnancy. No change in arterial O_2 content was observed during mild exercise in pregnant women (18, 279), but transcutaneous O_2 tensions increased slightly following exercise (223). Because these studies lacked controls it is not possible to conclude whether the changes are different from those in the nonpregnant state. Both pregnant and postpartum pygmy goats which underwent moderate short-term exercise showed a small decrease in arterial CO_2 tension, a small increase in O_2 content and no change in pH (93). Larger decreases in CO_2 tension were observed during prolonged moderate exercise in sheep (68, 73, 107, 212), and these were associated with a marked increase in pH (68, 73, 107) and with a decrease or slight increase in O_2 tension (68, 107).

However, in none of these studies were the blood gas values corrected for the exercise induced temperature increase. Blood obtained anaerobically and analyzed for respiratory gases at a temperature below that of the body provides falsely low O_2

and CO_2 tensions and a falsely high pH (300). Therefore consideration of exercise induced temperature changes is essential for a correct assessment of the blood gases in vivo. Lotgering et al (220) observed that when the blood gas values were corrected for the temperature changes in vivo, no significant changes occurred during short-term (10 min) exercise at 70 and 100% $\dot{V}O_2$ max in sheep. However, during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max the ewe's arterial O_2 tension increased 13% (to 116.7 Torr) and O_2 content 25% (to 3.3 $ml.dl^{-1}$), while CO_2 tension decreased 28% (to 27.6 Torr) and H^+ concentration decreased 22% (with a pH increase to 7.56). The increase in arterial O_2 content resulted largely from hemoconcentration. Figure 4 shows the changes in maternal respiratory blood gases during pregnancy at rest and during prolonged exercise. Recovery was virtually complete within 20 min.

Physical training during adolescence may increase vital capacity and total lung capacity (14), however during pregnancy it apparently has little affect on these functions, maximal breathing capacity, or respiratory frequency at rest or during and following exercise (169). Other respiratory variables have not been studied in relation to exercise training in pregnancy.

In conclusion, the marked hyperventilation during pregnancy results in a decrease in CO_2 tension and buffering capacity not only at rest but also during and following submaximal exercise. In other aspects respiration during exercise in pregnancy does not seem to differ from that in the nonpregnant state. Thus, it seems likely that the respiratory system does not limit working capacity during gestation, however, this awaits confirmation by controlled studies at maximal exercise levels.

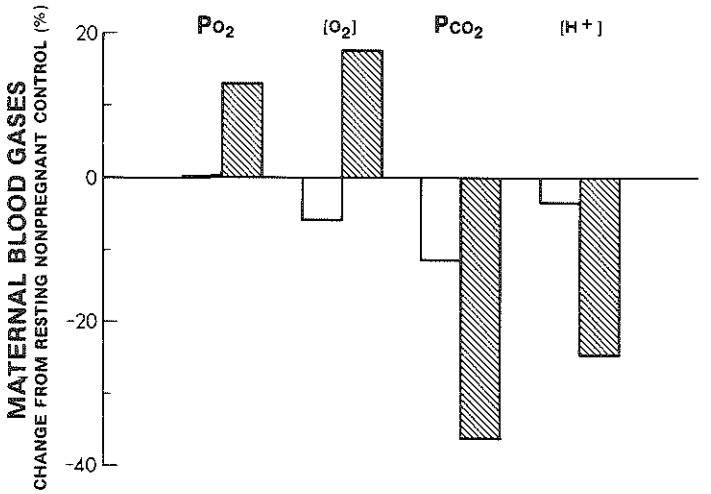

Figure 4. Changes in maternal respiratory blood gases during pregnancy at rest and during exercise. Approximate resting values for humans and goats (93, 205) with exercise responses for sheep (220) superimposed. Clear bars indicate rest, while shaded bars indicate exercise responses.

2.8 Circulation

Since 1915 when Lindhard (208) first observed increased cardiac output during pregnancy, many investigators have further explored the maternal circulatory adjustments. These have been recently reviewed by Metcalfe et al (232). Burwell et al (63), using the acetylene method, reported increased cardiac output with advancing gestational age reaching a maximum increase of about 50% at approximately 30 weeks. Later studies have used the direct Fick method (18, 145, 255, 279), dye dilution (3, 204, 323), thermodilution (298), and echocardiography (284) to measure cardiac output. It is now generally agreed that cardiac output is increased above nonpregnant levels by 12 weeks gestation, but opinions differ as to the subsequent changes. Cardiac output may further increase during the second trimester (145, 323), but several authors have reported no significant further change (16, 18, 204, 255, 279). Although earlier studies reported cardiac output decreasing during the third trimester to almost nonpregnant values near term, Lees et al (204) demonstrated that with the patient in the lateral position this fall did not occur. He suggested that decreased venous return in the supine position accounted for the lowered cardiac output observed during the third trimester in previous studies. Nonetheless, other investigators (16, 17, 323) have observed in the lateral and sitting positions during the third trimester a decrease in cardiac output to about 10% above nonpregnant values. In sheep (233) and goats (93) resting cardiac output during the third trimester remains 20 to 30% above nonpregnant or postpartum control values. Figure 5 shows the cardiac output and other cardiovascular changes during the third trimester, at rest and during exercise.

Burwell et al (63) reported a larger increase in cardiac output than in O_2 consumption during pregnancy, indicating diminished O_2 extraction. Subsequent studies (18, 145, 255, 279) have confirmed that in the first trimester cardiac output increases about 20% more than O_2 consumption. These studies also report that during the first trimester the arterio-mixed venous O_2 content difference (ΔO_2) is 11 to 27% lower than nonpregnant values, but gradually increases with advancing gestational age, reaching nonpregnant values near term. As oxygen consumption between 12 and 40 weeks gestation increases to an almost similar extent as ΔO_2, application of the Fick principle suggests that large changes in cardiac output during the last two trimesters are unlikely.

The changes in resting heart rate during pregnancy have been reviewed by Hytten and Leitch (168). There appears to be a marked heart rate increase early in pregnancy with a gradual further rise throughout gestation, so that near term the total increase equals about 15 bpm or 20% (Fig. 5). Because cardiac output increases more than heart rate, especially in early pregnancy, the largest increase in stroke volume must also occur in early pregnancy. Echocardiographic studies (284) show that during pregnancy stroke volume as well as the ejection fraction and the end diastolic volume increase while the end systolic volume remains unchanged.

The cardiovascular changes during exercise have been reviewed extensively (10, 14, 183, 283, 307, 325). During the first minute the cardiac output increase exceeds

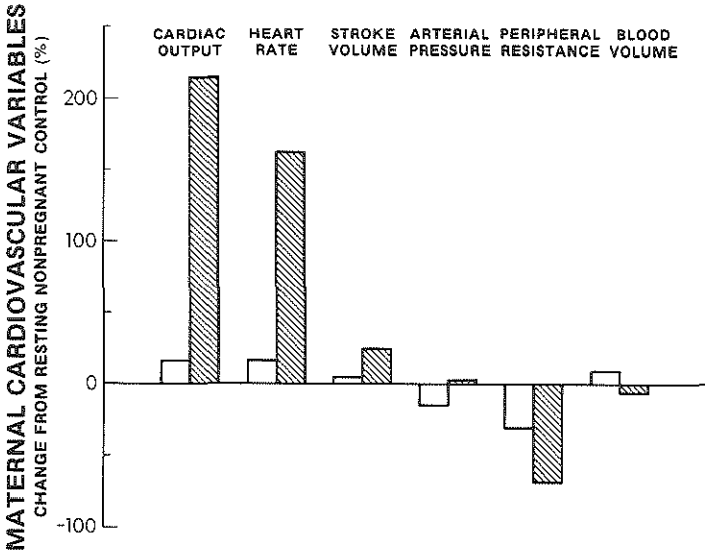

Figure 5. Cardiovascular changes during pregnancy at rest and during exercise. Approximate resting values from humans and goats (93, 193), with exercise responses for sheep (219) superimposed. Clear bars indicate rest, while shaded bars indicate exercise responses.

the increase in O_2 consumption as venous return increases immediately with exercise onset (138). However during "steady state" exercise, both cardiac output and O_2 extraction are almost linearly related to O_2 consumption under a wide variety of circumstances, because the factors which affect $\dot{V}O_2$ (e.g. age, sex, etc., see above) change both cardiac output and O_2 extraction. At submaximal workloads cardiac output is maintained by the interplay of heart rate and stroke volume which are functions of sympathetic control and venous return, respectively. The heart rate increase (up to 2 to 3 times resting value) is quantitatively more important than the stroke volume increase (up to 1.5 to 2 times resting value). Because resting stroke volume approaches its maximal value in the supine position, during supine exercise increased cardiac output must result mainly from an increase in heart rate.

The cardiac output response to exercise in pregnancy has been studied in humans (18, 101, 102, 139, 193, 197, 279, 306, 307, 322, 323), sheep (84, 219), and pygmy goats (93). Throughout gestation cardiac output values are higher than control values during (93) and following weightbearing exercise (197, 306, 307), as well as during handcrank (102) and bicycle exercise (139, 193, 322, 323). Bader et al (18, 279) observed a 13% lower cardiac output and a 29% higher arteriovenous O_2 content difference during exercise in the supine position near term than in early gestation, changes which probably reflect the decreased venous return in the supine position. Of the above studies during bicycle exercise only those of Ueland et al (322, 323) included both nonpregnant control and resting values. In pregnant

women the exercise induced increase in cardiac output was reported to be 33% higher (322, 323) during mild exercise and 24% lower during moderate exercise (323). Maximal changes have only been studied in sheep, with cardiac output increasing 2.7 fold under these conditions (219). However, whether this degree of increase differs from nonpregnant sheep is unknown. The above studies demonstrate that the increased O_2 consumption of exercise during pregnancy can be met by the combined effects of cardiac output and O_2 extraction, but the relative importance of each may vary with the circumstances, and their limits have not been studied in relation to pregnancy.

The maternal heart rate response to exercise during pregnancy has been studied in humans (9, 18, 30, 38, 86, 87, 103, 106, 110, 139, 147, 151, 169, 170, 193, 197, 206, 207, 223, 265, 273, 279, 303, 308, 323), sheep (73, 84, 107, 219), pygmy goats (93, 162, 163), and rats (333). Compared to a nonpregnant control group, during exercise heart rate during pregnancy is either slightly higher (38, 93, 139, 193) (Fig. 5) or not significantly different (30, 86, 87, 169, 170, 205, 206, 308, 323). It is also slightly higher or not significantly different from nonpregnant controls following exercise (38, 86, 87, 106, 147, 151, 169, 170, 197, 205, 206, 265, 308). The heart rate increase during or following exercise in pregnant women is similar to that in the controls (38, 86, 87, 93, 139, 151, 169, 170, 205, 206, 265, 308, 323). In pregnant sheep maximal heart rate averaged 215 bpm (219), but whether or not this value is increased above nonpregnant values is unknown. Maximal heart rate has not been studied during pregnancy in any other species, and deserves further investigation.

The exercise electrocardiogram in normal nonpregnant women may show a variety of changes including ST changes suggestive of ischemia (83). This finding led Cumming et al (83) to conclude that exercise electrocardiography in women is of limited value. Although during exercise in pregnant women ST changes are common (94), the physiological importance of these changes remains therefore unclear.

During pregnancy both heart rate and cardiac output are increased at rest, but the absolute increase during submaximal exercise is the same in pregnant and nonpregnant women and goats. Therefore, the same is true for stroke volume (93, 193, 323) (Fig. 5). Whether or not maximal stroke volume increases during pregnancy is unknown. As stroke volume largely depends on venous return, it is conceivable that the pregnancy induced hypervolemia results in increased maximal stroke volume. This could then result in increased maximal cardiac output and maximal oxygen consumption, but this has not been investigated.

Hytten en Leitch (168) have reviewed the resting arterial blood pressure changes during pregnancy in humans. In early and mid-gestation diastolic pressure decreases about 10% below nonpregnant values, while systolic pressure decreases only slightly. During the third trimester both pressures return towards nonpregnant values if supine hypotension is prevented. Sheep (233) and goats (93) do not show a clear gestational age trend and have slightly lower mean arterial pressures near term than postpartum. Total peripheral resistance in mid-pregnancy decreases as much as 30% in humans (18, 279), sheep (233), and goats (93) (Fig. 5). The

mechanisms of this decrease in vascular resistance are only partially elucidated, but may include the formation of an effective arteriovenous shunt by the placenta (61), decreased uterine and systemic vascular wall tension mediated by hormones (e.g. the progesterone to estrogen ratio) (210), and lowered viscosity associated with a fall in hematocrit (146).

Upon the initiation of exercise total peripheral resistance decreases immediately and is inversely related to O_2 consumption. The lowered resistance in the exercising muscles results from local vasodilatation, and is probably mainly of metabolic origin, whereas the increased resistance in nonexercising areas is mainly the result of sympathetic stimulation (283). The diastolic pressure remains virtually constant, whereas the systolic and thus the mean arterial pressures increase with workload intensity.

The arterial blood pressure response to exercise in pregnancy has been studied in humans (9, 18, 27, 106, 110, 197, 205, 206, 223, 265, 273, 279, 303, 308), sheep (73, 84, 107, 219) and goats (93, 162). These studies show an increase of up to 20% in mean arterial pressure during exercise (Fig. 5), mainly because of increased systolic pressure (18, 27, 205, 206, 273, 279, 303, 308). Although the systolic pressure increases with the level of exercise at low workloads in humans (27, 205, 206, 308), in sheep mean arterial pressure does not increase significantly when the exercise level is increased from 70 to 100% $\dot{V}O_2$ max, or when the duration of exercise is extended from 10 to 40 min (219). An increased pressure response to treadmill exercise has been reported in pregnant women (196) and goats (93), which may have resulted from a higher workload due to pregnancy weight gain. However, with one exception (205, 206) a slightly increased pressure in pregnant women has also been reported in response to bicycle exercise (27, 106, 308). Thus, the available evidence suggests a slightly increased pressure response to exercise of pregnant individuals over controls.

Because both the cardiac output increase and the arterial pressure response to submaximal exercise are only slightly altered by pregnancy, the exercise induced decrease in total peripheral resistance during pregnancy must be of a similar magnitude as in the nonpregnant state. The more marked decrease in total peripheral resistance calculated during weightbearing exercise in pygmy goats (93) probably reflects a higher workload rather than a pregnancy effect. The changes in total peripheral resistance during exercise in pregnancy affect cardiac output distribution, and will be discussed below.

Possibly related to the change in vascular wall tension is the decrease in fibrinolytic reactivity during both pregnancy and exercise. During the third trimester euglobulin lysis time at rest is markedly prolonged, while it is reduced with exercise. The response to exercise during pregnancy has been reported to be less pronounced (334) or not significantly different from that in controls (324). However, both the mechanism and the physiological implications of the observed difference in response are unclear.

Blood volume changes during pregnancy have been recently reviewed (150). With advancing gestation whole blood volume in humans increases gradually up to

50% near term, due to a 30 to 60% increase in plasma volume and a 20 to 30% increase in erythrocyte mass. The increases are less pronounced in some species (e.g. sheep). This hypervolemia may increase mean sytemic filling pressure which with the decreased peripheral resistance will mediate the increase in resting cardiac output and stroke volume during pregnancy.

During exercise plasma volume decreases as a function of exercise intensity, reaching a maximal reduction of 14% at about 60% $\dot{V}O_2$ max in man (134). The decrease occurs rapidly, is virtually complete within 10 min, and does not change further with exercise duration. Some workers (134, 307) consider the increased hydrostatic pressure to be the major force driving plasma filtrate across the capillary membrane in exercising muscles, while others (221) suggest a more important role for muscle tissue osmolality changes. This filtrate consists of water and electrolytes, and to a lesser extent of plasma proteins (136). The rise in hematocrit during exercise may also be partially caused by catecholamine induced red cell release by the spleen, however this has not been studied.

The hematocrit increases during exercise in pregnant sheep (68, 219), probably as the result of a decrease in plasma volume without a change in red cell mass (219) (Fig. 6). The 20% decrease in plasma volume observed in exercising pregnant sheep (Fig. 6) (219) was slightly larger than the maximal change observed in nonpregnant humans (134, 221) and was associated with a smaller increase in plasma protein concentration. Although one could speculate that these changes result from pregnancy induced hypervolemia and increased capillary permeability, it is more likely that these differences result from the species and methodology. Inherent in the calculation of plasma and red cell volumes from hematocrit and whole blood

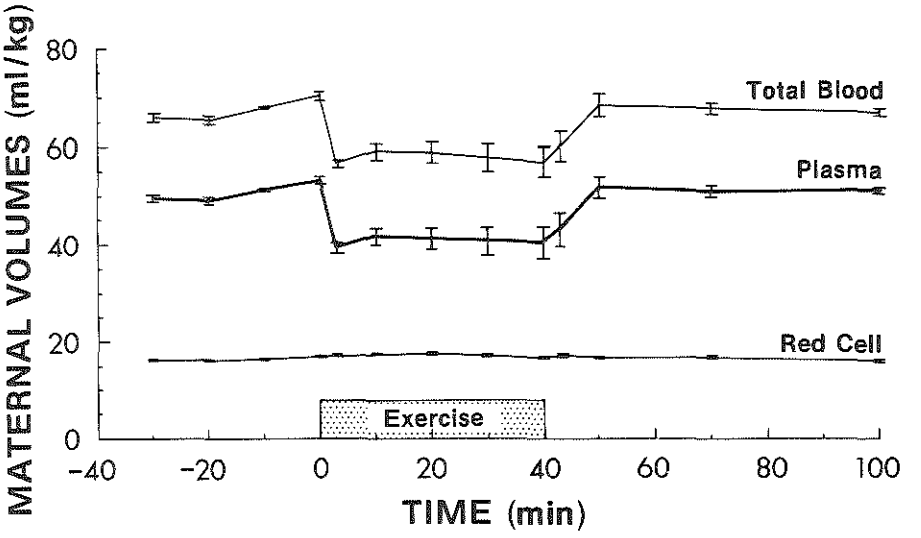

Figure 6. Changes in whole blood, plasma and red cell volumes during exercise in pregnant sheep (after Lotgering et al [219]).

volume is the assumption that the pool of circulating erythrocytes remains constant (219). However, the sheep spleen contains approximately 25% of the total red cell mass (326), and in dogs the erythrocytes sequestered in the spleen can be released by catecholamine infusion (20). If labeled red cells were released from the spleen at the onset of exercise the calculated whole blood and plasma volume decrease would be overestimated. Detailed studies are needed to provide information on the fluid shifts between the vascular and extravascular compartments during exercise in pregnancy.

The cardiovascular effects of physical training have been reviewed extensively (14, 75, 189, 283, 289, 291). Such training increases the maximal O_2 consumption mainly by increasing maximal cardiac output and to a lesser extent by increasing O_2 extraction (289). The increased maximal cardiac output results mainly from increased stroke volume, without a change in maximal heart rate. In trained individuals resting stroke volume also is increased as compared to nontrained controls, but resting cardiac output is not markedly different because heart rate decreases to a similar extent. Arterial pressure is maintained or reduced slightly below pretraining levels and blood volume rises (135). The increased stroke volume results from reduced peripheral resistance, improved myocardial contractility, and reduced sympathetic stimulation of the heart. Capillary density of the skeletal muscles and heart, whole blood and plasma volumes, and to a lesser extent red cell volume, increase during training, but the mechanisms involved in these changes are not fully understood. In trained individuals the cardiovascular responses are largely comparable to the responses of nontrained individuals at comparable physiological levels (% $\dot{V}O_2$ max) of exercise, but the adjustments may be faster (143). $\dot{V}O_2$ max is relatively unaffected by a variety of stresses, but stroke volume and heart rate are markedly affected (e.g., blood loss, dehydration, ambient temperature, fever, etc.). Therefore, the prediction of $\dot{V}O_2$ max from heart rate measurements during submaximal exercise is subject to error under such circumstances.

The cardiovascular effects of physical training during pregnancy have not been studied in detail. Curet et al (84) reported a higher resting cardiac output in mildly trained versus nontrained pregnant sheep, and a slightly greater increase in cardiac output following exercise in the trained ewes. However, the animals in both groups were not in a truly basal state (mean heart rate $>$ 115 bpm), and examination of their data reveals that the body weights in the trained group were higher than in the nontrained group. Thus, it is impossible to conclude from this study to what extent physical training during pregnancy affects resting cardiac output. A study in conditioned women (303) reported that heart rate at rest and following a treadmill test was lower as compared to controls, whereas blood pressure was unaffected. However, others have reported no significant differences in either heart rate or blood pressure between trained and nontrained pregnant women at rest or in response to bicycle exercise (110, 169). Wilson and Gisolfi (333) demonstrated in rats that vigorous training during pregnancy results in increased left ventricle to total heart weight ratio, similar to that observed in trained nonpregnant rats.

Apparently no other data on the effects of physical training during pregnancy are presently available.

The effect of exercise on pregnant cardiac patients has been discussed by numerous authors (29, 56, 62, 235, 277, 319, 321, 331, 335). Heart disease reduces cardiac reserve, but does not affect the plasma and blood volume increase during pregnancy (321). Such patients respond to exercise with greater tachycardia to compensate for the inability to increase stroke volume to the same extent as controls (56), demonstrating their lowered physical working capacity. Consequently, the demands of exercise may be excessive and can result in heart failure. A further discussion of exercise in pregnant cardiac patients is beyond the scope of this review.

The differences in resting values of several cardiovascular variables during pregnancy affect the absolute values obtained during exercise, but pregnancy does not seem to significantly alter the change at comparable submaximal exercise levels (% $\dot{V}O_2$ max). However, it is presently unknown to what extent pregnancy with or without training affects the cardiovascular responses to maximal exercise. Quantification of the cardiovascular changes during maximal exercise near term is important for a better understanding of the circulatory physiology and physiology of pregnancy.

2.9 Cardiac output distribution

The most striking change in blood flow distribution during pregnancy is the uterine blood flow increase with advancing gestational age. The methods used to measure uterine flow have been reviewed (55, 168, 275), and will be briefly summarized.

Indicator dilution techniques are based on the uterine arteriovenous difference of the test substance (nitrous oxide or antipyrine). The method requires sampling of uterine venous blood, which may not be adequately mixed, and steady state conditions. The value obtained represents the mean total uterine blood flow during the period of equilibration and sampling. A modified indicator dilution method uses radioactively labeled microspheres, the number of spheres trapped in the tissues after injection into the circulation being a measure of the flow to those tissues. In addition to requiring a steady state it requires adequate mixing of the spheres with the blood, an arterial blood reference sample, and the removal of the organ. The technique assumes the absence of shunts with a diameter larger than that of the microspheres, and only a limited number of injections can be made. The value obtained represents the mean flow to that tissue during the time of injection. It is the only method presently available to study the distribution of flow within an organ such as the uterus.

Electromagnetic and ultrasonic flowmeters measure instantaneous flow rate through a flowprobe of fixed diameter placed around a blood vessel, and thus are suited for studying dynamic changes. The flowprobe must be placed around the vessel and the tight fit required to obtain a good signal may compromise flow,

particularly if there is movement, as during exercise. Flowprobes are commonly placed around one branch of the uterine arteries, and provide only information about the portion of the vascular bed supplied by that vessel. Placement of a flowprobe around the common internal iliac artery, as present in the sheep, or the placement of probes on both main uterine arteries can increase that flow measured to over 95% of total (219).

These methods all require invasive techniques and therefore are not suitable for study in humans. Nonetheless, indicator dilution methods (11, 42, 234) and electromagnetic flowprobes (12) have been used acutely in pregnant women, however, only under stressful conditions or under anesthesia, and with the subject supine. Therefore the results from these studies showing a mean total uterine blood flow of 110 to 150 $ml.min^{-1}.kg$ total $uterus^{-1}$ may well underestimate total uterine flow under more physiologic conditions. Observations in chronically catheterized sheep using the antipyrine technique (166) and radioactively labeled microspheres (280), show values of approximately 240 $ml.min^{-1}.kg$ total $uterus^{-1}$, or absolute values near term of approximately 1300 $ml.min^{-1}$, a 50 to 60 fold increase above nonpregnant values. Blood flow to placental cotyledons increases with increasing fetal weight, whereas that to the myometrium and endometrium remains relatively constant (222), so that near term cotyledonary flow is approximately 85% of total uterine blood flow (272, 281). Because placental growth during the later part of gestation is small (225), the increase in cotyledonary flow during this period mainly reflects the increasing demands of the fetus. Acute studies (12, 229) showed a constant blood flow per kilogram of total uterine tissues during the course of gestation. However, in chronically instrumented animals the increase in uterine flow is less than the increase in total uterine or fetal weight, and blood flow per kilogram of total uterine contents or fetus decreases with advancing gestational age (166, 281).

Some of the factors which affect uterine blood flow have been reviewed (25, 26, 55, 275, 328). The large decrease in uterine vascular resistance during pregnancy probably results from vasodilation associated with increasing concentrations of estrogens produced by the fetoplacental unit and prostaglandins (PGE_2 and PGI_2) produced by the vessel wall. It is possible that estrogens exert their action by the mediation of prostaglandins, but the intermediate steps in the vascular smooth muscle relaxation have not been clearly identified. Although the uterine vasculature during pregnancy is less sensitive to the effects of vasoactive agents, it responds to circulating prostaglandins and catecholamines. The response of myoendometrial flow to catecholamines is similar in the pregnant and nonpregnant state, whereas cotyledonary flow is less sensitive (137). Decreases in uterine blood flow of as much as 20% have been reported to occur spontaneously (201, 327), and up to 50% in response to alkalosis (64, 253), hyperthermia (67, 253), and a variety of other stresses (240, 241, 302). It has been suggested that these vasoconstrictive occurrences are catecholamine mediated (149), but this needs further study.

The effects of physical exercise on cardiac output distribution have been extensively reviewed (14, 75, 76, 283, 325). The most striking change is the marked

increase in skeletal muscle blood flow, with a lesser rise in coronary flow, changes which reflect the increased metabolism in these tissues. The vasodilatation is thought to be mediated by several local metabolic factors including heat production, pH, O_2 tension, osmolality, and ATP and K^+ concentrations. The increased muscle flow is maintained primarily by the increase in cardiac output, and secondarily by flow restriction to regions which at rest receive a high blood flow and have low O_2 extraction, such as the splanchnic bed, kidneys, and resting muscle. This blood flow redistribution probably results from sympathetic nervous stimulation (283). There is a striking species difference in exercise response. While in man even mild exercise is associated with regional flow redistribution secondary to sympathetic stimulation, in dogs even prolonged heavy exercise fails to elicit such a response. However, when cardiac output is artificially reduced in dogs, the response is similar to that of man. Splanchnic, renal, and nonworking muscle blood flows decrease linearly with the exercise level (% $\dot{V}O_2$ max) in man, and the inverse relation between these flows and heart rate is consistent with the concept of sympathetic vasomotor regulation (283). Skin blood flow is subject to the same vasoconstrictive mechanisms, but also to poorly understood local factors which dilate these vessels in response to rising body or local skin temperatures. Local factors also reduce the vascular responsiveness of exercising muscles to sympathetic stimulation. Blood flow to other organs and tissues have been studied less completely, but appear to remain relatively constant. This indicates slightly increased vascular resistance in these tissues which is probably also from sympathetic origin. Posture normally does not seem to exert a major influence on regional blood flow.

The effect of exercise on uterine blood flow during pregnancy has been studied in humans (243), sheep (68, 73, 84, 212, 219, 254), and pygmy goats (162, 163). Using the disappearance of ^{24}Na injected into the myometrium, Morris et al (243) suggested a 25% decrease in perfusion of the human pregnant uterus during mild short-term bicycle exercise in the supine position. This probably represents an overestimate, because blood flow within the uterus is redistributed in response to exercise, favoring flow to the cotyledons at the cost of that to the myometrium (84, 163). Although posture itself has no major influence on exercise distribution of regional flow, it is conceivable that in the supine position the pressure of a large pregnant uterus would affect flow distribution. In contrast, Orr et al (254) using a doppler flow probe around a distal branch of the uterine artery, and Curet et al (84) using the microsphere technique, concluded that uterine blood flow in sheep remained constant during treadmill exercise. However, their measurements were made shortly after, rather than during, exercise and uterine flow returns rapidly to control levels when exercise is discontinued (see below). In preliminary studies Longo et al (212) reported a uterine flow decrease of up to 40% during prolonged exercise in sheep, while Hohimer et al (162) reported only minimal changes in goats. More recently Hohimer et al (163) using microspheres, and Clapp (73) and Chandler and Bell (68) using other indicator dilution methods, reported decreases in uterine blood flow up to 36% during exercise.

Lotgering et al (219) studied the total uterine blood flow response to different levels (% $\dot{V}O_2$ max) and durations of exercise in sheep using an electromagnetic flowmeter. The results are shown in Figure 7. Uterine blood flow decreased immediately at the onset of exercise, was significantly below control values throughout the exercise period, and returned to control values within 10 min of recovery. Uterine blood flow decreased 13% during a 10-min exercise period at 70% $\dot{V}O_2$ max, 17% during 10-min at 100% $\dot{V}O_2$ max, and 24% near the end of a 40-min period at 70% $\dot{V}O_2$ max. Although significantly different from the pre-exercise values, the differences between the three regimens were not significant, as a result of large spontaneous fluctuations. However, regression analysis showed a significant further decrease of flow with time, and flow varied linearly with heart rate (163, 220) (Fig. 8). Therefore, it seems likely that uterine blood flow decreases with both the level and the duration of exercise.

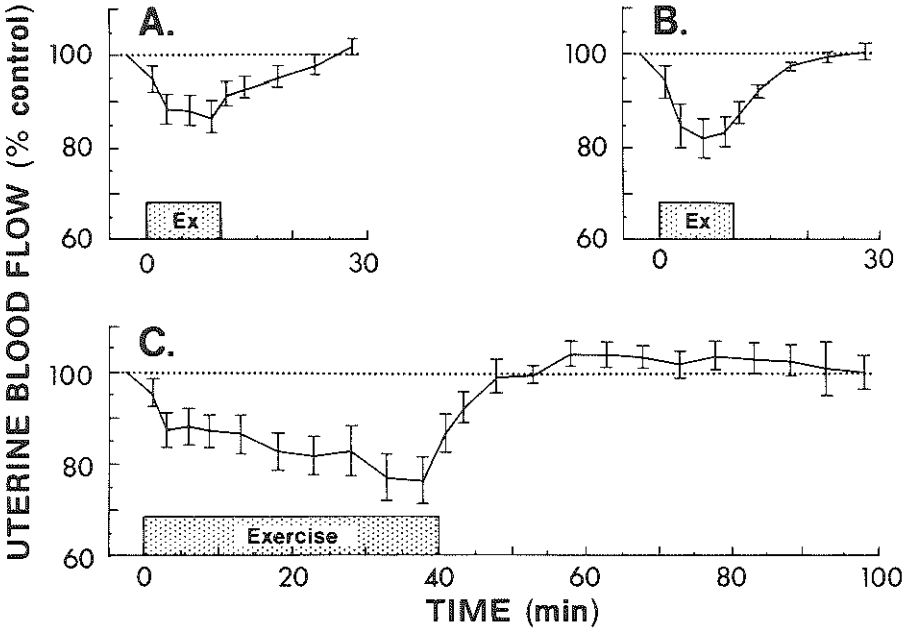

Figure 7. Uterine blood flow response to three different exercise regimens in pregnant sheep (after Lotgering et al [219]). A. 10 min exercise at 70% $\dot{V}O_2$ max, B. 10 min exercise at 100% $\dot{V}O_2$ max, C. 40 min exercise at 70% $\dot{V}O_2$ max.

The effects of increased sympathetic activity during exercise may be modified by local metabolic factors within the uterus. If this is true one would expect myometrial flow to behave like the flow to the splanchnic bed, whereas cotyledonary flow would decrease only to such an extent that the fetoplacental O_2 demands can still be met. There is some evidence that this is indeed the case. Blood flow within the uterus is redistributed to the cotyledons at the expense of the

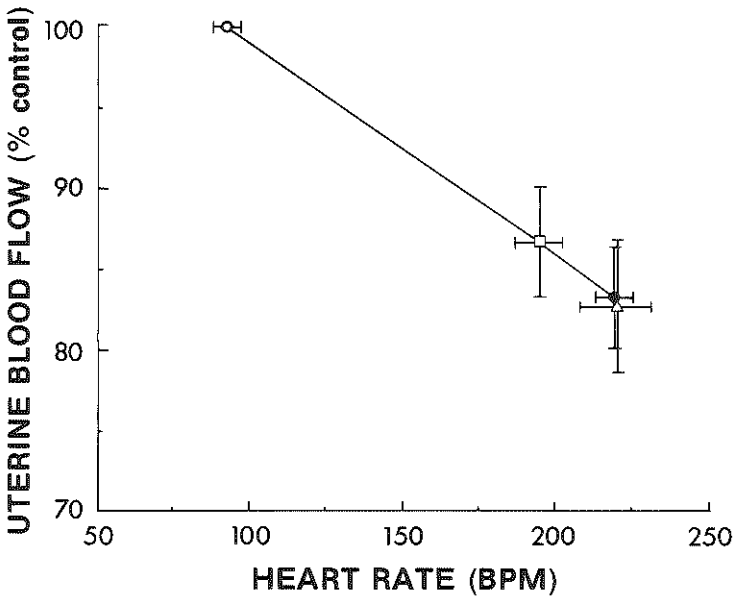

Figure 8. Relation between heart rate and total uterine blood flow in near term pregnant sheep (after Lotgering et al [219]). ○, *rest,* □, *10 min exercise at 70% $\dot{V}O_2$ max,* ●, *10 min exercise at 100% $\dot{V}O_2$ max,* △, 40 min exercise at 70% $\dot{V}O_2$ *max.*

myometrium, both during catecholamine infusion (72, 282) as well as during (163), and following (84) exercise. Although the exercise induced increase in uterine vascular resistance probably results from active vasoconstriction caused by increased sympathetic activity, this has not been demonstrated.

The distribution of blood flow to other organs during gestation has been studied in sheep with the use of microspheres (280). Flow to the mammary glands increases and flow to the liver and adrenal glands decreases, while renal flow does not change significantly. In contrast, studies in humans show increased renal flow during gestation (209), and there is evidence that skin blood flow also rises (311). From the observation that urinary 5-hydroxy-indolacidic acid following exercise is more reduced in pregnant women than in controls, it has been suggested that the decrease in visceral blood flow during exercise is more pronounced in pregnant women (95). However, more direct measurements are required to demonstrate a reduction in visceral flow.

Orr et al (254) reported significant increases in carotid and iliac artery flow in both pregnant and nonpregnant ewes, and Curet et al (84) found no change in renal flow following exercise in pregnant sheep, but made no comparison with nonpregnant ewes. The perfusion of other organs has not been studied in relation to exercise during pregnancy. Thus, with the exception of uterine flow, the extent to which regional blood flow distribution during exercise is altered by pregnancy is largely unknown.

Physical training results in increased maximal O_2 consumption, and a larger resting stroke volume and lower heart rate at rest (75). It is thought that training results in lower (and certain diseases, e.g. mitral stenosis, in higher) sympathetic vasomotor activity at similar absolute exercise levels. However, sympathetic activity is similar in response to comparable physiologic levels of exercise (% $\dot{V}O_2$ max), and results in similar effects on regional flow distribution (75).

The effects of physical training on recovery uterine and renal blood flows have been studied in sheep by Curet et al (84). They did not observe a difference between trained and nontrained animals, but the exercise was not quantified in physiological terms, and their groups were too small to allow a definite conclusion.

From the above it appears that blood flow to all tissues is regulated mainly by the opposing local metabolic vasodilatory factors and sympathetic nervous vasoconstriction. The local metabolic factors seem to dominate the cardiac output distribution during pregnancy, exercise, and the combination of exercise and pregnancy, but further studies are needed to verify whether or not uterine blood flow regulation during exercise in pregnancy is indeed dominated by local metabolic factors. The study of these factors and the chain of events leading to uterine blood flow regulation may not only be of academic interest, but could reveal information relevant for uncovering the pathogenesis of preeclampsia and fetal growth retardation.

2.10 Uterine oxygen consumption

Uterine O_2 consumption increases during pregnancy in response to the increasing demands of the growing conceptus, as demonstrated in humans (12), sheep, and goats (166, 229, 244). With advancing gestational age the uterine arteriovenous O_2 difference rises slightly (244) or markedly (from 0.5 to 5 $ml.dl^{-1}$) (166). Thus, uterine O_2 consumption increases more than would be expected on the basis of the blood flow increase alone. Acute studies showed a constant uterine blood flow and O_2 consumption per kilogram of tissue with advancing gestational age (12, 229), where studies in chronically catheterized sheep showed a decreasing uterine blood flow but constant (244) or increasing (166) O_2 consumption per kilogram of tissue. Near term the mean O_2 consumption of total uterine contents (myoendometrium, placenta and fetus), fetus, and placenta plus myoendometrium are approximately 9.9, 7.1, and 14.1 $ml.min^{-1}.kg^{-1}$, respectively (229).

Uterine O_2 consumption during exercise has not been studied in pregnant humans, but does not change significantly in response to prolonged submaximal treadmill exercise in sheep (68, 73, 220). While total uterine blood flow in these studies was markedly reduced, O_2 consumption was maintained as the result of hemoconcentration and increased O_2 extraction (220). However, it is unknown whether O_2 extraction increases to the same extent in myoendometrium and placental cotyledons. During maternal exercise cotyledonary flow decreases less than myoendometrial flow (84, 163). Thus, in order to maintain the same metabolic rate during exercise the myoendometrium must increase its O_2 extraction to a

greater extent than that of the cotyledons. However, this has not been demonstrated and it is conceivable that myoendometrial O_2 consumption during exercise decreases below resting values. The intriguing problem of autoregulation of blood flow and O_2 consumption within the uterus needs further study.

Training results in a smaller physiologic burden of any given exercise task, consequently sympathetic stimulation will be less. Therefore it is likely that physical training reduces the observed effects of a given task on uterine circulation and O_2 extraction, but this has not been demonstrated.

2.11 Summary of maternal responses

Table 2 summarizes some of the major changes associated with pregnancy, exercise and training. Because of differences between studies and/or species the table represents only approximate responses. The specific physiologic adjustments are detailed above. In addition, the important issue of the maternal effects of exercise in pregnant women with endocrinologic or cardiovascular disorders has not been addressed.

Table 2. Maximal responses of selected maternal physiologic variables to pregnancy, exercise, and training.

	Near term Pregnancy*	Exercise*	Exercise during Pregnancy^x	Training^x	Training and Pregnancy†
O_2 consumption	↑ or ↑↑	↑↑↑	↑	↑↑	↑ ?
Respiratory minute volume	↑	↑↑↑	↑ ?	↑	—
Tidal volume	↑	↑↑↑	↑ ?	— ?	— ?
Respiratory frequency	—	↑↑↑	— ?	↑	—
Cardiac output	↑ or ↑↑	↑↑↑	↑ ?	↑ or ↑↑	↑ ?
Stroke volume	↑	↑↑	↑ ?	↑ or↑↑	↑ ?
Heart rate	↑	↑↑↑	— ?	—	— ?
Mean arterial pressure	— or ↓	↑	— ?	—	— ?
Plasma volume	↑ or ↑↑↑ o	↓	— ?	—	— ?
Uterine blood flow	↑↑↑	↓↓↓ ?	↑ ?	— ?	— ?

*Change from nonpregnant, nontrained, resting values; ^{x}change from nonpregnant, nontrained, exercise values; †change from pregnant, nontrained, exercise values; o marked species difference; ? doubtful or unknown; — change <5%; ↑ or ↓ increase or decrease of 6-20%; ↑↑ or ↓↓ 21-40%; ↑↑↑ or ↓↓↓ >40%.

3. Placental responses

The placenta has a multitude of functions which are only partially understood. Barron (21) has recently reviewed the discovery of its respiratory function. As early as 1796 Erasmus Darwin deducted from the color difference of the umbilical vessels that the placenta is a respiratory organ for the fetus, and Paul Zweifel established definitive proof in 1876. Because its anatomy and physiology are so interwoven

with those of the mother and fetus, its physiologic functions are difficult to study separately.

One can measure the uptake of oxygen and nutrients simultaneously of the uterus as a whole as well as of the fetus. By substraction one can calculate the O_2 and nutrient consumption of the uteroplacental mass. Meschia et al (227) have estimated that the uterus plus placenta consumes half of the O_2 and two thirds of the glucose metabolized by the uterus as a whole, indicating that the O_2 and glucose consumptions are respectively 5 and 10 times as high as in the fetus on a per kilogram basis. With the available techniques one cannot separate placental metabolism from that of the myoendometrium under in vivo conditions. The myoendometrium has a mass about equal to the placenta, but is probably metabolically less active. Thus the weight specific values for placental metabolism are probably even higher than the values presented above. The effect of exercise on placental metabolism is unknown. Because total uterine oxygen consumption does not change significantly during exercise (68, 73, 220), placental metabolism also is probably not markedly affected.

The placenta uses several mechanisms to transport various substances: diffusion, facilitated diffusion, and active transport (90). Oxygen exchanges across the placenta by passive diffusion and may be considered flow limited. Theoretical analysis (213) suggests that both the magnitude and distribution of maternal and fetal placental blood flows as well as maternal and fetal hemoglobin concentrations will markedly affect placental O_2 transport, whereas only striking differences in the physical chemical characteristics of the membranes will affect oxygen diffusion. The placental diffusing capacity for O_2 cannot be quantified practically, but the diffusing capacity for carbon monoxide ($^{D}P_{CO}$), a diffusion limited gas, provides a method to measure steady state gas exchange. The $^{D}P_{CO}$ is sensitive to anatomical changes (exchange area and membrane thickness), but relatively insensitive to changes in blood flow and unevenness of distribution (214). Near term $^{D}P_{CO}$ expressed in terms of fetal weight is relatively high in small species (37), but placental diffusing capacity does not markedly decrease during the last two months of sheep pregnancy (211).

Acute exercise does not affect $^{D}P_{CO}$ in sheep (220), suggesting that the factors which affect diffusion do not change acutely during exercise. However, this does not exclude the possibility that the amount of O_2 crossing the placenta per minute is reduced during exercise, as this is affected by the increased maternal hemoglobin concentration, maternal P_{50}, temperature, and the Bohr effect, and by reductions in uterine and umbilical blood flows. However, it is impossible to assess accurately the extent to which O_2 transfer will be affected. The observation that total uterine O_2 consumption does not decrease, even during prolonged exhaustive exercise (68, 73, 220), suggests the absence of a major alteration in placental O_2 transfer.

In guinea pigs which were exercised throughout gestation Gilbert et al (130) and Nelson et al (247) observed as much as 34% lower $^{D}P_{CO}$ values than in controls, the decrease being a function of the amount of daily exercise. In other chronically exercised guinea pigs, Smith et al (305) demonstrated a linear relation between

placental diffusing capacity and maternal and fetal surface area per unit volume of placenta. The reason for the smaller placental exchange areas in chronically exercised guinea pigs is unknown. Although theoretically O_2 transfer is affected by the decrease in surface area, it remains unclear whether O_2 transfer limitation caused the reduced birth weight observed in these fetuses.

Glucose diffuses across the placenta by facilitated diffusion and the carrier system has been studied in detail (35, 36, 181, 338). Glucose uptake increases rapidly with increasing maternal blood concentrations until the concentration is reached where the "carriers" are saturated and above which the rate of transport is slower. Other D-monosaccharides compete for the same stereospecific carrier, and estrogens and progesterones inhibit the transport, but the system is sodium independent. In chronically catheterized sheep at rest, glucose uptake by the fetus and the uteroplacental mass equals 28% and 72%, respectively, of the total uterine glucose uptake (304). Theoretical analysis (304) suggests that the net glucose transfer to the fetus is relatively insensitive to changes in uterine or umbilical blood flow. This seems to be confirmed by observations during prolonged exercise in sheep (68), where total uterine glucose uptake remained constant as the result of increased glucose extraction despite a significant reduction in uterine blood flow. However, this may also have resulted from the increased transplacental glucose gradient during exercise. Although the constant uterine glucose uptake suggests that the uptake of the different compartments (myoendometrium, placenta, and fetus) also remains constant, this has not been investigated.

Lactate is the second most important substrate for fetal metabolism (22). It also diffuses across the placenta by a facilitated process (239), but its carrier system has not been studied in the same detail as for glucose, nor is it known whether or not glucose and lactate compete for the same carrier. However, rather than transferring from maternal blood, most of the lactate metabolized by the fetus is produced by the placenta. A recent study in chronically catheterized near term sheep (309) showed an uteroplacental lactate production of 11.8 $mg.min^{-1}$, 5.0 $mg.min^{-1}$ of which was taken up by the mother and 6.5 $mg.min^{-1}$ (or 1.7 $mg.min^{-1}.kg^{-1}$) by the fetus. During prolonged exercise in sheep, Chandler and Bell (68) observed only an insignificant reduction in maternal lactate uptake. It seems likely that this resulted from the increased maternal blood concentration and the resulting decreased placental-maternal lactate gradient. It is unknown to what extent placental lactate production is affected by exercise or what its physiological consequences might be.

Acetate is an important fuel for the resting ewe, but its role in fetal-placental metabolism is largely unknown. Nonetheless, uterine acetate uptake is unaffected by exercise in sheep (68).

Amino acids are used not only for protein synthesis, but also for combustion in both placenta and fetus, and they are actively transported by the placenta (22, 90). It would be of interest to know whether this energy requiring transport mechanism is influenced by exercise, but this possibility has not been investigated. The placental transport of lipids, ions, steroids, and proteins also has not been studied in relation to exercise.

Little is known about the placenta as a heat exchanger. Because the fetal body temperature is higher than that of the mother (see below), some limitation to heat transfer must exist. In contrast with earlier calculations (153), Adamsons (4) and Abrams et al (1) concluded that the largest proportion of the heat produced by the fetus diffuses to the mother across the placenta and a smaller proportion across the fetal skin, amniotic fluid, and uterine wall. In these calculations heat transfer is considered as being limited by blood flow, and there is some experimental evidence to support this concept (4, 242). However, the heat production by the placenta and the extent to which it affects the fetomaternal heat transfer is unknown. It is also unknown to what extent placental heat production and transport are affected by maternal exercise. We will discuss in greater detail below the factors which may affect placental heat transfer.

In conclusion, the effects of acute and chronic exercise on metabolic and transport functions of the placenta have been investigated only to a limited extent, and the effects on the placental endocrine function are unknown.

4. Fetal responses

The fetus requires a continuous supply of oxygen and nutrients for "basal" metabolism, growth and body movements, and its demands increase steadily with advancing gestation. A prolonged severe reduction in its supply will result in fetal demise, but less severe reductions (e.g. during labor) normally do not cause apparent damage. Our present understanding of the fetal adjustments and tolerance limits is still limited, and several factors are responsible for this lack of knowledge.

First there is the absence of accurate yet sensitive criteria for tolerance limits. Permanent damage to a structure or function proves that tolerance was exceeded, but this criterion is relatively insensitive because small changes in structure or function may be undetectable. Growth retardation is proof of chronic adjustments within such limits, but this criterion lacks sensitivity because of the large normal variation. Physiologic variables such as heart rate, oxygen consumption, and oxygen, substrate, or hormone concentrations are more sensitive to changes, but rather than giving any information as to the fetal tolerance, they represent mainly temporary adjustments.

However, even obtaining information about such basic physiologic variables is not easy in the fetus because it is so well protected from ingress. With the use of ultrasound techniques one can study heart rate, breathing and body movements, and certain body structures in the human fetus with relative ease. Most other functions cannot be studied in humans because they require invasive techniques which limit their use to experimental animals. With the introduction of the technique of chronic catheterization of the fetus by Meschia, Barron, and their colleagues (228), it became possible to study adaptive changes in certain laboratory animals to a variety of stresses without the disadvantages of anesthesia or acute surgical stress.

4.1 Oxygen consumption

Fetal oxygen consumption can be calculated from umbilical blood flow and arteriovenous O_2 content difference, and the methods involved are similar to those used in the uterine circulation. The O_2 consumption value obtained under chronic conditions in the fetal lamb during the third trimester is approximately 8.0 $ml.min^{-1}.kg\ fetus^{-1}$ (22, 216). To what extent it normally fluctuates or demonstrates a diurnal rhythm is presently unknown. It is also unknown how the fetus regulates its O_2 consumption, although it is known to be affected by several factors. Moderate maternal hypoxia ($P_{O_2} = 50$ Torr) does not affect fetal O_2 consumption, but more severe maternal hypoxia reduces it by up to 40%, resulting from a marked decrease in O_2 extraction without a change in umbilical blood flow (258). With shortterm infusion of norepinephrine (217) or long-term infusion of triiodothyronine (218) into the fetus, fetal O_2 consumption increases about 25%. However, in contrast to hypoxia this is associated with an increase in umbilical blood flow and no change in O_2 extraction. To what extent catecholamine changes within the physiologic range affect fetal O_2 consumption has not been investigated. Nor have the effects of such large changes in O_2 consumption on fetal heat production, and consequently fetal temperature, been explored. This may be important for the interpretation of respiratory blood gas values, as will be discussed below.

Clapp (73) observed a slight and insignificant increase in umbilical O_2 uptake in sheep during exhaustive maternal exercise, despite a 28% decrease in total uterine blood flow. The constant O_2 uptake resulted from a 10% decrease in umbilical blood flow and a concomitant 13% increase in O_2 extraction. This observation is supported by the finding of constant total uterine O_2 consumption during maternal exercise (68, 73, 220), and suggests the absence of major changes in fetal or uteroplacental O_2 consumption.

According to the van 't Hoff-Arrhenius law, the O_2 consumption of both total uterine contents and fetus should rise during the exercise induced hyperthermia. Assuming a Q_{10} of 2 to 3, Lotgering et al (220) calculated from their results that O_2 consumption of the fetus should have increased 9 to 16% during prolonged exercise, and that of the placenta and uterine wall 11 to 18%, but we observed an increase of only 6% in O_2 consumption of the total uterine contents. Although the 6% increase may possibly not be significantly different from the value expected from the calculated Q_{10} effect, other changes in the fetus may also affect its O_2 consumption. Substrate limitation or pH change may prevent expression of the increased enzymatic reaction rates as expected from the Q_{10} effect. In addition, it has been argued that the van 't Hoff-Arrhenius law may be masked by central nervous system regulation, as has been shown to occur in poikilothermic species (57). Therefore it is impossible to assess accurately whether the fetal and placental O_2 requirements are met or whether they should have increased during maternal exercise. Fetal O_2 tension and saturation are poor predictors of fetal O_2 consumption (69, 259), and cannot give much information as to what extent the O_2 requirements are met. Therefore, changes in fetal O_2 tension or content without other signs of hypoxia or "stress" merely reflect temporary adjustments.

4.2 Fetal metabolism and endocrinology

The intricacies of fetal metabolism are complex. Substrates are used not only for "basal" metabolism and heat production, but also for growth and muscular activities. Furthermore, it is conceivable that under certain conditions the fetus relies temporarily on anaerobic metabolism (258).

Battaglia and Meschia (22) have calculated that about 65% of the caloric expenditure in the sheep fetus is used for oxidative metabolism and 35% for growth. If one assumes that the O_2 consumption per kilogram tissue is the same in other species with different growth rates, it follows that fetal oxidative metabolism may vary considerably, but this has not been systematically studied. It is unknown to what extent the fetus may change its energy requirements during maternal exercise by, for example, temporarily slowing its growth. The respiratory quotient of the umbilical circulation is 0.94 (176). It probably is falsely low because relatively large amounts of carbon and nitrogen are incorporated in the growing organism, and indicates the predominant metabolism of carbohydrates and amino acids.

Glucose crosses the placenta by facilitated diffusion, thus the rate is dependent upon the concentration in maternal blood. The fetal blood glucose concentration, the umbilical glucose uptake, and the glucose to O_2 quotient decrease during maternal fasting, changes which are probably mediated by a lower fetal insulin concentration (294). Physical or verbal stress of the ewe does not affect the plasma glucose and insulin concentrations in mother or fetus (295). However, during prolonged moderate treadmill exercise in sheep, fetal blood glucose concentrations increase up to 75%, with less pronounced changes occuring during shortterm or mild exercise (68, 220). Uterine glucose uptake remains constant during prolonged exercise despite a marked decrease in blood flow because glucose extraction increases to the same proportion (68). Probably, the increased glucose extraction results simply from the increased maternal to fetal glucose gradient during exercise (from 2.0 to 3.1 $mMol.l^{-1}$).

Although fetal lactate concentration is about twice that of the mother, under normal conditions this does not result from anaerobic metabolism (60). The placenta produces large quantities of lactate (probably from maternal glucose), releasing it into the maternal and fetal circulations. Fetal metabolism of this lactate may constitute 25% of fetal O_2 consumption (22). To what extent fetal anaerobic metabolism may produce lactate under stressed conditions is unknown. Fetal lactate concentrations increase during prolonged moderate exercise by up to 50 to 70%, but do not change significantly during short-term or mild exercise (68, 73, 220). Chandler and Bell (68) observed that during prolonged moderate exercise in sheep the normal placental release of lactate into the maternal circulation was reversed with lactate being taken up by the pregnant uterus. Although the change in uterine lactate uptake during exercise was not significant in this study, it seems likely that the markedly increased maternal lactate concentration (to 2.5 from 0.9 $mMol.l^{-1}$) with the consequent decrease in the feto-maternal concentration gradient will affect uterine uptake. Clapp (73) observed continued lactate uptake in the

umbilical circulation during prolonged exhaustive exercise, but the data are inadequate to allow one to calculate quantitative changes. The persistence of fetal lactate uptake and absence of a change in base excess during exercise suggest that the increased fetal lactate concentration results from fetal adaptation to increased maternal concentrations rather than from anaerobic metabolism. Clapp (73) reported a 40% increase in fetal lactate to pyruvate ratio, which is smaller than the 70% increase in the mother. This also suggests adjustments to elevated maternal concentrations rather than anaerobic metabolism, and thus these changes probably do not affect the health of the fetus.

Amino acids are actively transported across the placenta, with about 60% being used as fuel and 40% for growth in the fetal lamb (22). Free fatty acids represent only a negligible fraction of the total caloric intake in the sheep fetus in which fat accounts for 2% of the body weight at term, but may be more important in other species such as man, in which it constitutes 16% of birth weight. The uterine uptake of acetate during maternal exercise in sheep does not change significantly (68). The uterine or fetal uptake of other fatty acids and amino acids has not been studied in relation to exercise.

Although the fetal glucose and lactate concentrations are affected by maternal exercise, it is unknown to what extent the relative contribution of the different substrates to fetal aerobic metabolism or growth are affected. This is also true for the role of anaerobic metabolism under these conditions. The effects of physical training on fetal metabolism have not been studied, but its possible effects on fetal growth are discussed below.

4.3 Body temperature

The regulation of fetal temperature has not been studied in detail. Under normal resting conditions the fetal temperature in the human (4), baboon (240), and sheep (1) is about 0.5°C higher than that of the mother. When the maternal temperature rises, that of the fetus increases more slowly and the normal fetal-maternal temperature gradient diminishes (67) or reverses (4). When maternal temperature plateaus after artificial heating (4) or pyrogen injection (1), the temperature gradient returns to near normal values, and when maternal temperature falls during the recovery phase, the fetal temperature decrease is delayed resulting in an increased fetal to maternal difference (4, 67).

Fetal and maternal placental blood flows also can affect fetal temperature. Morishima et al (242) demonstrated an increased fetal-maternal temperature gradient with partial occlusion of either the umbilical cord, the maternal aorta or the inferior vena cava, as well as with uterine contractions. It is possible that the fetal changes observed during heating result partially from changes in uterine blood flow (67).

Lotgering et al (220) demonstrated that during maternal exercise the fetal temperature changes (Fig. 2) are comparable to those observed during maternal heating (4). The fetal temperature lags behind that of the relatively rapidly changing

maternal temperature at the onset and cessation of exercise. This results in a smaller or reversed temperature gradient during the onset and a larger gradient immediately following exercise (Fig. 2). The reversal of the temperature gradient is most pronounced soon after the exercise onset when the maternal temperature increases rapidly, but becomes progressively less as the maternal temperature plateaus. With heavier exercise (100 vs 70% $\dot{V}O_2$ max) the maternal temperature increases more rapidly, resulting in a larger reversal of the temperature gradient (Fig. 2). Following prolonged (40 min) exhaustive exercise at 70% $\dot{V}O_2$ max, return to a normal fetal temperature and a normal temperature gradient required over one hour.

Heat is stored in the body core during exercise at rates proportional to exercise intensity. Because the fetal heat exchange is linked to maternal temperature by flow limited diffusion, the fetal temperature will increase with that of the mother. A mathematical model of placental heat transfer developed by Schröder et al (296) correctly predicted the fetal temperature changes from the changes in maternal temperature and uterine blood flow when variables such as fetal metabolism were assumed constant (220). Further calculations (Schröder and Gilbert, unpublished data) suggest that maternal temperature is the major determinant, while changes in fetal metabolism or uterine blood flow of up to 50% will change fetal temperature by less than 0.3°C. However, the extent to which the fetus can regulate its body temperature is unknown, and the relative importance of the factors which influence fetal temperature has not been established experimentally. Although the changes in fetal temperature suggest a passive dependence on the factors cited above, the constancy of the temperature gradient under steady state conditions suggests the presence of homeostatic mechanisms.

The physiologic implications of the changes in maternal and fetal temperatures are only partially understood. A possible Q_{10} effect has been discussed above. Temperature changes will affect placental and fetal respiratory gas transport, as a temperature increase shifts the oxyhemoglobin dissociation curve to the right. This will tend to increase oxygen unloading in the fetal tissues. A mathematical model of placental O_2 transport (213) suggests that during maternal heating as in exercise, the larger shift in maternal than in fetal P_{50} will result in only a small increase in placental O_2 exchange and fetal O_2 tension. During exercise this effect is obviously opposed by other factors, as fetal O_2 tension decreases. One such factor is uterine blood flow, which is not only reduced by the sympathetic stimulation of exercise but also by the temperature increase (67).

Knowledge of the temperature is essential for the correct interpretation of fetal blood gas measurements. As noted above, blood obtained anaerobically and analyzed for respiratory blood gases at a temperature below that of the body shows a rise in pH and a fall in O_2 and CO_2 tensions (300). The failure to correct for a 1°C increase has been estimated to result in about a 1.9 and 2.7 Torr underestimate for fetal O_2 and CO_2 tensions respectively, while pH will be 0.015 units too high (220). Although the fetal-maternal temperature gradient seems to be rather constant under steady state conditions, all factors which change maternal temperature,

uterine or umbilical blood flows, or fetal metabolism, potentially affect the temperature gradient, especially in the nonsteady state. Unfortunately, this is often not taken into account in studies of fetal blood gas values.

Acute maternal exercise affects both fetal temperature and the fetal-maternal temperature difference. To what extent physical training during pregnancy affects fetal temperature or placental heat exchange has not been investigated. Although it is conceivable that a reduced placental diffusion area, as observed in chronically exercised guinea pigs (305) may reduce heat transfer, its influence on fetal temperature has not been studied.

The physiological implications of hyperthermia for fetal growth and metabolism are largely unknown and deserve further study. The possible teratogenic effect of hyperthermia is discussed below.

4.4 Respiration and blood gases

The fetus exchanges oxygen and carbon dioxide with the mother by transplacental passive diffusion, and this exchange is affected by several factors including maternal and fetal placental blood flows, arterial O_2 tensions, and hemoglobin concentrations (213).

Several studies in exercising sheep (68, 73, 107, 212) have reported significant decreases in fetal arterial O_2 tension and content of as much as 25%. These studies failed to correct the respiratory blood gas values for the fetal temperature changes in vivo, which resulted in underestimates of fetal O_2 and CO_2 tensions and overestimates of pH values. Failure to make these temperature corrections largely explains the difference in respiratory blood gas values between these studies and those of Lotgering et al (220). In this latter study (220) fetal arterial O_2 and CO_2 tensions and O_2 content decreased with the level and the duration of exercise, but the values differed significantly from control only when the ewes were run to exhaustion. Near the end of prolonged (40 min) exercise at 70% $\dot{V}O_2$ max, ascending aortic O_2 tension decreased 3.0 Torr, to 23.2 Torr from a value of 26.2 Torr at rest. CO_2 tension decreased 4.5 Torr from 54.1 Torr at rest and O_2 content decreased 1.5 $ml.dl^{-1}$ from 5.8 $ml.dl^{-1}$ at rest, while pH increased 0.02 units. Figure 9 shows the percent changes in fetal blood gases under these circumstances. With the exception of O_2 content, all blood gases returned to control values within 20 min of termination of exercise. The cause of the decrease in fetal O_2 tension and content during prolonged maternal exercise is not entirely clear. Theoretical calculations suggest that 30% of the decrease in O_2 saturation can be accounted for by the temperature and Bohr shifts of the oxyhemoglobin saturation curve (220). The remaining 70% of the decrease in O_2 saturation and the 3 Torr decrease in O_2 tension probably results largely from the decrease in placental blood flow.

Although the fetus receives its oxygen via the placenta instead of its lungs, it makes respiratory like movements. Boddy and Dawes (43, 44) have reviewed the physiological aspects of fetal breathing movements. They can be regarded as isometric muscular activity with a frequency of 30 to 70 bpm in humans and 60 to

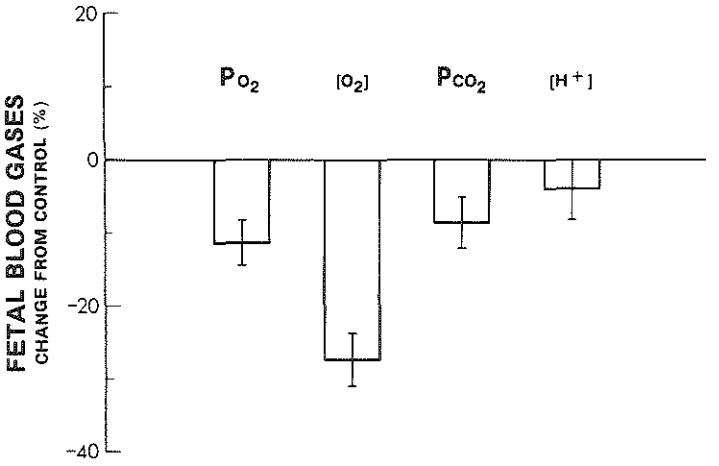

Figure 9. Percent changes in fetal sheep respiratory blood gases and hydrogen ion concentrations during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max (after Lotgering et al [220]).

120 bpm in sheep, and episodes of breathing and apnea follow each other frequently but variably. Breathing movements are present 40% of the time in sheep and 75% of the time in humans. They show a pronounced diurnal rhythm with a rise during the day to a peak shortly after dusk, and in the fetal lamb they coincide with rapid eye movement sleep. While the respiratory like movements do not affect the blood gas values, they are affected by several factors including O_2 and CO_2 tensions, and glucose and catecholamine concentrations. A decrease in fetal O_2 tension reduces fetal breathing movements, whereas an increase in CO_2 tension stimulates them.

The possible effects of maternal exercise on fetal respiratory like activity has been studied following, but not during, exercise and the results are conflicting. In the human fetus, Maršál et al (223, 224) observed an increase in the percentage of time spent breathing, with an increase in irregular movements and a decrease in periodic and apneaic episodes following short-term bicycle exercise. In contrast, Platt and Artal (268) observed a variable response following short term mild treadmill exercise. In the latter study, the maternal glucose concentration did not change with exercise, which probably reflects the low workload, and was unrelated to the fetal breathing response. However, these workers reported an increased maternal epinephrine concentration associated with increased repiratory like activity. This suggests that the workload (% $\dot{V}O_2$ max) may affect the fetal breathing response, possibly mediated by changes in uterine blood flow and/or fetal respiratory blood gases, but this has not been studied. Fetal breathing movements normally do not affect fetal O_2 tension although they must increase fetal O_2 consumption, but this increase probably is quantitatively of little importance. Other physiological implications of possible changes in fetal breathing movements are presently unclear.

Although fetal O_2 tension and content decrease with exercise, this does not necessarily indicate decreased fetal O_2 consumption or "stress", as was mentioned earlier. The regulation of fetal O_2 tension and content and its relation to metabolism needs further investigation. Further studies are also needed to investigate the importance of fetal respiratory like activity as an index for "fetal distress", its physiological implications, and regulatory mechanisms. All these unresolved questions are important for the correct interpretation of the observations during strenuous maternal exercise.

4.5 Circulation

Because of its accessibility, fetal heart rate monitoring is widely used in clinical obstetrics. Presently, several characteristics are used to detect "distress" and to predict fetal outcome. Empirically associated with "fetal distress" are severe brady- and tachycardia (<100 or >180 bpm), loss of variability (bandwidth <5 bpm, zero crossings <2 per min), the absence of accelerations, and the presence of "late" or "unfavorable" "variable" decelerations (120). The physiologic basis for these changes is only partially understood and its discussion is clearly beyond the scope of this review. Only large changes in mean heart rate are probably quantitatively important for the oxygen delivery to the tissues (see below). Fetal heart rate usually decreases in response to catecholamines (78, 182, 217), whereas hypoxia has beeen reported both to increase (48) and to decrease (241) mean heart rate, while others failed to find a regular change in fetal heart rate during even severe hypoxia (24, 263). Fetal heart rate increases in response to the pyrogen induced rise in body temperature, but is variable when the temperature plateaus (152). This has also been observed during direct heating of the fetus (Schröder and Gilbert, personal communication).

The human fetal heart rate response to maternal exercise has been studied repeatedly since Hon and Wohlgemuth (164) proposed it as a clinical test for "uteroplacental insufficiency". However, in most of these studies (103-105, 164, 198, 223, 224, 265, 269, 270, 308, 315) the measurements were made only prior to and following a mild to moderate exercise stress of short duration rather than during the exercise per se. Apparently only small and insignificant changes in mean fetal heart rate following such exercise were noted in these studies, and the heart rate patterns were inconclusive as to possible "distress", when the above cited criteria were applied. Recently, Dale et al (89) reported transient fetal bradycardia during short-term treadmill exercise. In contrast, Sibley et al (303) reported a slightly higher fetal heart rate during short-term treadmill exercise, as compared to baseline and recovery values, but they did not compare the mean values. This is also true for a study (154) in which higher heart rates were found during the recovery from prolonged, moderately strenuous, weightbearing exercise (1.5 miles jogging) in 7 women. Accelerations persisted during the recovery period, which presumably is a sign of "fetal well-being" (203). One study reported the changes in fetal heart rate both during and following 25 min bicycle exercise at about 70% $\dot{V}O_2$ max (77). The

auscultated heart rate demonstrated only a mean 3-4 bpm increase during and following exercise, which is physiologically insignificant. In sheep, mean fetal heart rate is unaffected by short-term exercise even at $\dot{V}O_2$ max (220). In contrast, Emmanouilides et al (107) observed an increase in heart rate (to 171 bpm from 152) during prolonged exercise, however, other investigators (73, 220, 256) have not confirmed this observation. Because the ewes in two of these studies (73, 220) reached exhaustion, a difference in the level of exercise cannot explain the observed difference in response.

To date other fetal cardiovascular variables which require invasive techniques have only been studied in experimental animals. Because the fetal heart operates near the plateau of its Starling function curve (129) fetal heart rate changes may not affect cardiac output, although Rudolph and Heymann (286) suggest a relation between fetal heart rate and cardiac output. Fetal cardiac output increases as a function of body weight, being about 500 $ml.min^{-1}.kg^{-1}$ in sheep (215, 285), and rhesus monkeys (24). Moderate degrees of hypoxia may (24) or may not (215) decrease fetal cardiac output, and catecholamines do not seem to effect it (216). In the only study (220) of fetal cardiac output during maternal exercise it was not affected by short-term exercise. The effects of prolonged and/or exhaustive exercise have not been studied.

The increase in cardiac output with advancing gestation is associated with a similar increase in blood volume. Whole blood and plasma volumes are largely proportional to body weight and are approximately 140 $ml.kg\ fetus^{-1}$ (80, 252) and 100 $ml.kg^{-1}$ (66), respectively, in sheep. Hypoxia may increase the fetal hematocrit (301). Lotgering et al (220) observed that fetal blood and plasma volumes are unaffected by prolonged, exhaustive, treadmill exercise in the ewe, which confirms the absence of a change in hematocrit as observed previously (68).

The distribution of cardiac output to the fetal organs is practically constant throughout gestation, with the exception of increased lung, brain, and intestinal flow (285). About 40% of cardiac output, the largest proportion to a single organ, is directed to the placenta, i.e. 200 $ml.min^{-1}.kg^{-1}$ in rhesus monkey (24), and sheep (32, 229, 263, 285). Measurements in human fetuses with the use of ultrasound have suggested a much lower flow (120 $ml.min^{-1}.kg^{-1}$) (131). This value depends critically upon an accurate measurement of the blood flow velocity and the vessel diameter, and further studies are needed to verify the technique. Hypoxia has been reported to decrease umbilical blood flow 60% in rhesus monkeys (24), but this fall has not been confirmed in sheep (215, 263). Catecholamines increase umbilical flow (217). In addition, changes in blood flow distribution to other organs (lungs, heart, brain, and adrenals) have been reported in response to hypoxia and norepinephrine infusion (24, 215, 217, 263). Umbilical blood flow in sheep is unaffected by short-term exercise at 70 and 100% $\dot{V}O_2$ max (220), and by prolonged but mild maternal exercise (73), but it has been reported to fall 10% in response to prolonged exhaustive exercise (73). However, the latter observation needs to be confirmed by further studies because the resting umbilical blood flow value of 354 $ml.min^{-1}.kg^{-1}$ in this study was higher than accepted normal values. Lotgering et al (220) found no

change in cardiac output distribution to other organs during short-term maternal exercise, but prolonged exercise was not studied.

Fetal blood pressure gradually increases with advancing gestational age, reaching a value of about 40 mm Hg in near term sheep, when corrected for amniotic fluid pressure (115). Mean arterial pressure increases in response to norepinephrine infusion (217), whereas hypoxia may increase (215, 263) or not affect it (241). Fetal arterial blood pressure was found unaffected by short-term (220) as well as prolonged exercise in sheep (73, 107, 220, 256), suggesting no great release of catecholamines.

Although the studies of fetal cardiovascular responses during maternal exercise are limited, the available evidence suggests the absence of major changes. In turn this suggests the absence of hypoxia or other "stress". In addition, only small and insignificant increases in fetal catecholamine concentrations have been noted in fetal sheep in response to both short-term (220), and prolonged exercise (161, 220, 256). Further studies are required to investigate the fetal cardiovascular response to prolonged exhaustive exercise especially in humans, and should include measurements during exercise.

Table 3 summarizes some of the fetal variables in relation to prolonged and strenuous exercise. Most of the results as shown in the table are derived from studies in sheep. Extrapolation to humans or other species may not be legitimate for several reasons, including differences in body position, relative fetal size, uterine contractility, and responsiveness to hormonal changes.

Table 3. Maximal responses of selected fetal physiologic variables to maternal exercise.

O_2 consumption	—
Cardiac output	—
Heart rate	— or ↑
Mean arterial pressure	—
Plasma volume	—
Umbilical blood flow	↓
Arterial O_2 tension	↓
„ O_2 content	↓↓
„ CO_2 tension	↓
„ H^+ concentration	—
„ catecholamine concentration	— ?

? doubtful, — change <5%, ↑ or ↓ increase or decrease of 6-20%, ↓↓ 21-40%.

5. *Fetal outcome*

Fetal outcome shows a wide normal variation as it is the resultant of a large number of variables including genetic factors, socio-economic factors, physical and health characteristics of the mother prior to and during pregnancy, food intake, exposure to drugs and toxic agents, "stress", obstetrical care, exercise, et cetera.

Definitive conclusions regarding any individual factor should be based on prospective studies which include well matched controls.

Although several retrospective studies in humans have reported the effects of physical activity on fetal outcome in terms of perinatal mortality, birthweight, and congenital abnormalities, none of these studies include well matched controls. The question of how physical activity may affect parturition or fetal outcome has been approached from several directions including the study of exercise restriction, mild exercise and childbirth preparation classes, heavy exercise in professional and amateur sportswomen, and the effects of employment. In experimental animals controlled studies have reported the effects of exercise on birth weight, subsequent organ and function development, and congenital abnormalities. In addition some related influences such as heat exposure have also been explored.

Although several studies have suggested a beneficial effect of rest in late pregnancy (see Briend [50, 51]), this has not been established, and adverse effects of immobilization on fetal outcome have also been suggested. Michel and Fritz-Niggli (236) observed that growth retardation and congenital abnormalities doubled in mice fetuses from mothers that were restrained from 10 to 30 min daily throughout pregnancy. However, it is questionable if this was related to the restraint per se or to the associated "stress", caused by fear and handling. Further studies are needed to detect whether or not reduction of physical activity per se does indeed affect fetal outcome.

Several authors have discussed the physiologic aspects of exercise and/or childbirth preparation classes on maternal "fitness", backache, pelvic function, or fetal well-being (41, 91, 127, 132, 155, 226, 232, 245, 257, 312, 340). In general, they conclude that mild exercise has beneficial effects on the mother, and apparently does not harm the fetus. Although some of these studies suggest a better fetal outcome in women who participated in such mild exercise programs, the evidence is not unequivocal. Erkkola (111) observed slightly higher birth weights in mothers with a high "fitness score" (or work capacity), but this was not confirmed by Pomerance et al (271). No correlation was found between "physical fitness" and the condition of the fetus as judged from Apgar score (111, 271) or umbilical artery pH (113). It appears obvious, however, that mild exercise normally does not harm the fetus as almost all pregnant women exercise mildly or moderately as part of their daily activities. In addition, a study in mice showed that voluntarily exercising mice did not have more abnormal offspring than their less physically active controls (188).

The effects of moderate or strenuous exercise during pregnancy have mainly been studied in athletes (65, 88, 89, 98, 108, 117, 154, 194, 250, 267, 287, 288, 339). Although smaller pelvis have been reported in women athletes (195), all of the above studies reported normal or improved parturition and fetal outcome. However, they must be interpreted with care as these studies were retrospective and/or uncontrolled. In addition, all of the women were probably in excellent condition prior to pregnancy, and if they maintained their traning program during pregnancy they increased their workload due to weight gain. In a first attempt to

prospectively study effects of maternal exercise on fetal outcome, Clapp and Dickstein (74) observed no effect on fetal outcome of preconceptual exercise, but an increased incidence of low birth weight infants from mothers who regularly performed vigorous exercise during pregnancy. However, as the authors point out themselves, the findings of their study must be interpreted with caution because the accuracy of the data is limited. To our knowledge the effects of a progressive workload during pregnancy or the effects of strenuous or exhaustive exercise have not been studied in women with a sedentary lifestyle prior to pregnancy. Strenuous physical activity during gestation is common in several species. Large game mammals and their predators are active up to the moment of birth. This is also true for dogs and some other domestic animals, and pregnant mares are allowed to race competitively as long as there is a reasonable chance of winning (59). This suggests, but obviously does not prove, that strenuous activity during pregnancy normally does not adversely affect fetal outcome in many species.

In contrast, adverse effects on fetal outcome have been reported in pregnant animals which were forced to exercise strenuously during pregnancy in a laboratory environment. Intrauterine growth retardation with 8% weight reduction was reported in controlled studies in mice (317) and guinea pigs (247). In the same mice Terada (317) noted an increased incidence of resorbed and macerated fetuses, but this obervation has not been confirmed. In rats forced to swim (207) fetal weights were 6% lower, but in rats that were forced to run (40) growth was not retarded. Dhindsa et al (93) reported fetal growth retardation with 20% weight reduction in exercising pygmy goats with multiple pregnancies, but a 12% increase in goats with singleton pregnancy, and it is not clear whether the study included proper controls. Studies in swine (144) did not show any effect of moderate daily exercise on fetal weight. Restriction of physical activities may also cause fetal growth retardation (188). One wonders if the "stress" of fear and handling, related to forced exercise in a laboratory environment, may not have contributed to the growth retardation rather than the exercise per se. Also, it is conceivable that fetal growth retardation occurs more easily in animals with a high fetal to maternal body weight ratio.

Several studies have reported the organ weights and function development in neonates born from exercised mothers. Nelson et al (247) observed brain "sparing" effect in the growth retarded offspring of very strenuously exercised guinea pigs, immediately after birth. However, body and organ weight were not different from controls in neonatal rats born from exercised mothers (40, 178, 261, 262, 333). Wilson and Gisolfi (333) reported that $\dot{V}O_2$ max, heart rate, blood pressure, myocardial blood flow, myocardial capillary density, and fiber to capillary ratio were not different from controls in male offspring of exercised rat mothers, although they did observe a lower number of fiber areas in the right ventricle of these neonates. These observations are in contrast with those of Pařízková (260, 262), who reported increased capillary density, fiber to capillary ratio, and a decreased diffusion distance in hearts from neonatal rats born from exercised mothers. Bonner et al (47) observed that cultured myocardial cells from offspring of exercised rat mothers were larger in size, showed an increased percentage of

contracting cells, and beat at a slower rate than cells from controls, but this experiment has not been repeated. Other unconfirmed studies have reported altered lipid metabolism (262), decreased glucose and higher insulin concentrations (207), delayed ossification (317), poorer motor performance (178), and unchanged skeletal muscle myosin ATP-ase, succinate dehydrogenase and phosphofructokinase in offspring of chronically exercised mothers (79). Further studies will be required to investigate the intriguing possibility that maternal exercise may affect certain fetal functions and to confirm the above observations.

Certain activities may be potentially harmful to the fetus for other reasons than the exercise per se. This is obviously true for contact sports in which violent jostling or compression are common such as wrestling, skiing, rodeo riding, and equestrian activities. A slightly increased incidence (6/136) of fetal anomalies, (skeletal malformations, cardiac defects and two minor defects) has been reported in pregnant scuba divers (45). Some of the possible contributing physiologic aspects were recently discussed (248), but the mechanisms and the observation itself need further study. Mountaineering, with its additional risks of hypoxia, irradiation and hypothermia, has not been studied in pregnant women.

Many factors other than physical activity per se may influence the results of studies of employment effects on fetal outcome. A cross-cultural study on 202 societies revealed that the most common activity pattern was that of continuing full duties until term (180). Some obstetricians (199) advise women to stop working several weeks before term, but the American College of Obstetricians and Gynecologists does not consider normal pregnancy to be a reason to discontinue work (6, 230). However, several studies reported at 150 to 400 gram lower mean birthweight in humans (246, 316) or a 6 to 10% higher incidence of low birth weight infants (123, 278) in offspring of working mothers. In one study fetal growth retardation was strongly related to low prepregnancy weight (246), which may reflect poor nutritional status, while in another study growth retardation occurred only when the caloric intake was below 70% of WHO/FAO standards (316). The other two studies did not investigate this possibility. Fox et al (123) reported several other complications in pregnancy, delivery and fetal outcome of pregnant active duty military personnel. They observed a 7% higher incidence of toxemia and perinatal mortality, which has not been confirmed by the other studies, and a 10% higher incidence of premature delivery. However the study was only matched for parity and race, and larger retrospective studies showed that the prematurity rate in employed women is increased less than 2% (8), or unaffected (5), while Gofin (133) reported a slightly higher incidence of low birth weight infants in employed women than in controls. Overall, these retrospective studies do not suggest major effects of maternal employment on fetal outcome, although one cannot exclude the possibility of growth retardation and premature delivery. Further well matched prospective studies are necessary to confirm any such relation and to investigate to what extent the physical activity per se is responsible for any such effects.

Heat stress has also been associated with a variety of congenital abnormalities in humans (121, 124, 237, 306). All these reports were from small retrospective studies

and the fever was caused by pyrogens. Therefore, the results may well reflect the influence of an infectious disease rather than the heat stress per se. Heat stress has been reported to cause fetal growth retardation (156), intrauterine death (202), and central nervous defects (99) in several species. However, although a maternal temperature increase of 2°C has been reported to cause microcephaly in guinea pigs (99), an increased incidence of congenital abnormalities has not been reported in association with maternal exercise. It should be noted, however, that this has not been systematically investigated on a large scale. Maternal "stress" and epinephrine infusion can cause behavioral changes in the offspring (see Crist and Hulka [81], and Huttunen [167]), but only one study in rats (178) has suggested that such changes may occur in offspring from exercised mothers.

In conclusion, there is some evidence that chronic maternal physical activity is associated with a small reduction in birth weight in some species, but further well controlled prospective studies are needed to confirm this. The mechanisms which account for this effect are presently unresolved, but possibilities include decreases in uterine blood flow, substrate availability, or placental exchange area. Presently there is neither sufficient evidence nor physiologic basis to suggest other adverse effects of maternal exercise on fetal and neonatal outcome.

6. Summary and recommendations

Strenuous exercise has numerous effects upon the pregnant mother, the developing fetus, and the placenta. In turn pregnancy has certain effects upon the performance of physical activity. Pregnancy markedly affects maternal metabolism and the cardiovascular and respiratory systems. The increase in O_2 consumption results almost exclusively from the increased tissue mass. A higher cardiorespiratory effort is required to perform a given amount of external work during pregnancy. The possibility that maximal O_2 consumption may increase during pregnancy has not been studied in depth, yet it is a most important variable as it puts other changes in perspective. One would expect that the increase in energy requirements of a given task as induced by the weight gain would result in some training effect, unless a more sedentary lifestyle is adopted. The latter probably occurs commonly in some western societies, but reflects a cultural rather than a physiological phenomenon, as in many other societies and species little reduction in physical activity is seen.

In contrast to the profound alterations in the mother and despite reductions in uterine blood flow during maternal exercise, physiologic changes in the fetus are small. During prolonged exhaustive exercise the fetal temperature increases 1 to 2°C and relatively small changes occur in the blood concentrations of oxygen and substrates. Despite these modifications there is little evidence for significant alteration in fetal metabolism, cardiovascular hemodynamics, or blood catecholamine concentrations. This suggests that acute exercise normally does not represent a major hypoxic or other stress for the fetus. However, most of this

information is derived from studies in sheep, and species differences may exist. It is conceivable that the upright position and the increased uterine contractility and magnitude of autonomic response, and increased susceptibility to venous pooling in humans may affect the fetal responses differently. Further studies, especially under strenuous circumstances, are needed to investigate this possibility.

Virtually nothing is known about the physiologic effects of chronic exercise on the fetus. The most likely effect on the fetus seems to be a relatively small reduction in birth weight, at least in some species. However, this needs to be further investigated. The data presently available do not allow any conclusions as to other possible effects of chronic exercise on the fetus. Further studies are needed for a more complete understanding of the mechanisms involved in the remarkably effective homeostatic mechanisms which account for such relatively small changes in the fetus during maternal exercise.

Investigation into the effects of exercise on pregnancy, the fetus, and the newborn should include both prospective epidemiologic studies in humans and laboratory studies in humans as well as in experimental animals. Recommendations for some of these studies have recently been made by a study group under the aegis of the National Institute of Child Health and Human Development (231). The possible beneficial effects of supervised exercise programs for the mother and infant mandate investigation of human volunteers. However, because of possible undesirable effects of extreme (for that individual) exercise upon maternal and fetal health, careful attention must be paid to optimal experimental design and proper precautions, and to obtaining fully informed consent. Also, the stress of exercise should be defined in physiologic terms (percentage of maximal O_2 consumption, or less ideally, percentage of age predicted maximal heart rate).

Some questions that need further study include: 1) Does pregnancy affect the efficiency of the muscle cells or just the mechanical efficiency, and if so, by what mechanism? 2) To what extent does an increase in maternal oxygen consumption compensate for the increased demands or reduced efficiency due to pregnancy weight gain? 3) What is the effect of training on the maximal oxygen consumption? 4) Is the relation between heart rate and oxygen consumption altered by pregnancy? 5) Is fetal growth in humans indeed affected by physical training during pregnancy? 6) If so, what is the critical amount of exercise, how is fetal body composition affected, and what are the mechanisms involved? 7) Does placental weight correlate with maternal exercise and if so, is this cause or effect of fetal growth retardation? 8) To what extent does maternal condition and/or training prior to gestation, rather than during pregnancy, affect the course and outcome of pregnancy? 9) Is there a minimal or maximal amount of exercise that should not be exceeded during pregnancy because of the risks involved for mother and fetus? 10) To what extent does maternal behavior during pregnancy (e.g. exercise) affect behavior or development of the offspring, and what are the possible mechanisms?

A related issue concerns how the responses of the pregnant woman and her fetus are affected by factors which interact with exercise, such as decreased maternal blood volume, increased environmental temperature and/or humidity, decreased

environmental oxygen tension, compromised nutritional status, or complications of pregnancy such as anemia, heart disease, pregnancy induced hypertension, and diabetes mellitus.

The question of how physical activity during pregnancy relates to the health of a woman and her child are of fundamental importance, both in countries where women exercise for pleasure, as well as in populations where work, even during pregnancy, is a necessity of life. However, exercise should be considered as only one of the many variables that affect maternal health and fetal and neonatal development. Studies of the effects of exercise should be carefully controlled for other factors, which include individual factors such as physical condition and nutritional status, environmental factors such as altitude and ambient temperature, and socio-economic variables such as medical care.

Further studies concerning the interactions of pregnancy and physical activity will contribute to the knowledge of physiology of pregnancy as well as of exercise, thus providing basic information for both obstetricians and sports-physicians and consequently improving the care for, and the well being of, the pregnant mother and her infant.

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CHAPTER TWO

Exercise responses in pregnant sheep: Oxygen consumption, uterine blood flow, and blood volume

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1. Abstract

In an attempt to explore the acute maternal responses to exercise we measured oxygen consumption, uterine blood flow, and blood volume in 13 chronically catheterized pregnant sheep at rest and while exercising on a treadmill. With maximal exercise O_2 consumption increased 5.6 times, from a resting value of 5.8 (± 0.3 SEM) to 32.1 (± 2.8) ml.min^{-1}.kg^{-1}; cardiac output increased 2.7 times, from 149 (± 8) to 404 (± 32) ml.min^{-1}.kg^{-1}; and arteriovenous oxygen content difference increased 2.1 times, from 3.9 (± 0.2) to 8.0 (± 0.4) ml.dl^{-1}. Total uterine blood flow decreased from a mean resting value of 292 (± 6) to 222 (± 19) ml.min^{-1}.kg fetus^{-1} near exhaustion during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. Maternal blood volume decreased 14% ($p < 0.01$), from 67.5 (± 3.7) to 57.8 (± 3.6) ml.kg^{-1} during this exercise period, with a 20% decrease in plasma volume without a change in red cell volume. We conclude that uterine blood flow decreases during maternal exercise, however, hemoconcentration helps to maintain a relatively constant oxygen delivery to the uterus.

2. Introduction

Pregnancy is associated with physiologic changes in the cardiovascular system, such as increases in oxygen consumption (33), heart rate, cardiac output, uterine blood flow, and blood volume (30). Acute exercise also increases oxygen consumption, heart rate, and cardiac output, while it decreases blood volume (24). In addition, the redistribution of blood flow to exercising muscle away from the

splanchnic bed might compromise uterine blood flow and the delivery of oxygen and other substrates to the fetus. The question thus arises as to what extent these competing demands of exercise and pregnancy can result in restricted working capacity or compromised fetal oxygenation in the exercising pregnant subject.

Working capacity is highly dependent on physical condition, which can be described most accurately by the level of maximal oxygen consumption ($\dot{V}O_2$ max) (2). Previous reports of uterine blood flow during pregnancy have expressed the workload in absolute values which, according to Åstrand and Rodahl (2), may be quite meaningless. Workload should be expressed in physiologic terms, such as percent of maximal oxygen consumption or heart rate.

According to some investigators treadmill exercise does not affect uterine blood flow in pregnant sheep and goats (8, 28) but others report a decrease of as much as 28% (7) to 36% (6). These unexplained variations in reported uterine blood flow may possibly have resulted from differences in exercise regimens and in physical condition of the animals, or from stresses indirectly related to the exercise.

Plasma volumes have been shown to decrease as much as 17% during exercise in nonpregnant humans (24), but have not previously been studied in pregnancy. A similar decrease in plasma volume with hemoconcentration in pregnant individuals would help to maintain oxygen flow to the pregnant uterus during exercise despite a decrease in uterine blood flow.

In an effort to determine the magnitude of the cardiovascular responses to maternal exercise we studied oxygen consumption, heart rate, cardiac output, uterine blood flow, and blood volume in chronically catheterized sheep. We attempted to minimize interanimal variation by studying uterine blood flow at standard physiological levels of exercise (70 and 100% $\dot{V}O_2$ max), in well-conditioned animals.

3. *Methods*

3.1 *Principle of Method*

In a preliminary experiment, we determined $\dot{V}O_2$ max in each ewe by measuring cardiac output and arteriovenous O_2 content difference during intermittent 10-min exercise periods at increasing levels. Subsequently we measured uterine blood flow during three different exercise regimens: shortlasting exercise (10 min) at 70 and 100% $\dot{V}O_2$ max and prolonged exercise (40 min) at 70% $\dot{V}O_2$ max. We measured blood and plasma volumes during a single 40-min exercise period at 70% $\dot{V}O_2$ max.

3.2 *Animals*

We studied 13 pregnant ewes of mixed western breed with single fetus of 117 to 138 days gestation (term 147 days). The mean maternal weight was 55.6 ($\pm$ 3.8 SEM) kg, while the mean fetal weight was 3.5 ($\pm$ 0.3) kg. All animals appeared

healthy at the time of the experiments. We conditioned the ewes to walk on the treadmill at various speeds for short intermittent periods, totaling 10 min each, for 1 week prior to surgery. During this time the ewes were fed alfalfa pellets ad libitum. Twelve to twenty-four hours prior to surgery the animals were taken off food, but water remained available.

3.3 Surgery

We performed surgery in two steps, using spinal anesthesia supplemented with pentobarbital. First we used a midline abdominal incision to insert catheters into the fetus to study placental respiratory gas exchange and fetal oxygenation (23).

Immediately following the first phase of surgery we placed the ewe in the right lateral position for a retroperitoneal approach to the distal branches of the aorta. We made a 15 cm hockeystick shaped incision in the skin of the left flank, the curvature being 2 to 3 cm medial to the iliac crest. Oblique and transverse abdominal muscles were incised parallel to the muscle fibres and the distal branches of the aorta exposed by blunt dissection. Figure 1A illustrates the anatomy and nomenclature of the branches, modified after Fuller et al (12). We dissected free and doubly ligated the right lateral and dorsal sacral arteries. We dissected the left lateral sacral artery free for about 2 cm and introduced a Tygon catheter (1.5 mm od), advancing the tip into the common internal iliac artery. We than placed an electromagnetic flowprobe (Micron Instruments Inc., Los Angeles, CA) of appropriate size (8 mm id) around the common internal iliac artery. Figure 1B shows the position of the flowprobe, catheter, and ligatures. The catheter and probe leads were tied to adjacent tissue for fixation, and we placed a Penrose drain close to the flowprobe. We passed the probe leads, catheter, and drain, as well as the catheters from the first phase of surgery, subcutaneously through the same stab wound in the maternal flank into a nylon pouch attached to the skin for protection.

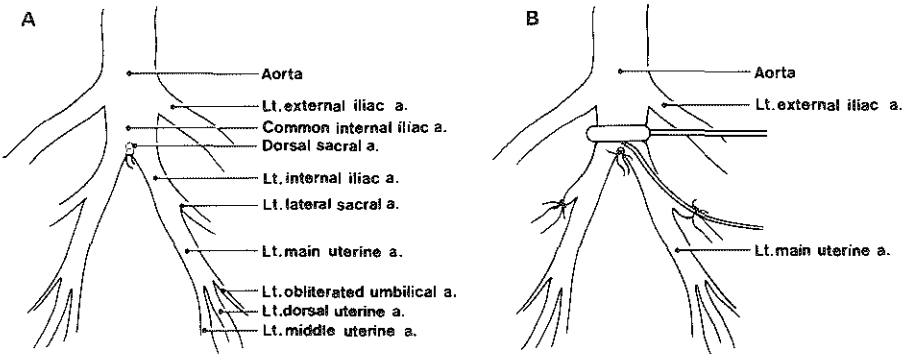

Figure 1. A. Schematic representation of the distal branches of the aorta in sheep (Modified after [12]). B. Schematic representation of the position of the electromagnetic flowprobe, catheter, and ligatures.

Over the course of three days we gradually removed the drain. Each day we flushed the catheters with 2 ml of saline containing 1 unit of heparin per ml, injected 500 mg of Ampicillin into the amniotic fluid and administered 2 ml of Combiotic intramuscularly to the ewe. By palpation and visual inspection at autopsy we verified both the position of the catheters and the flowprobe, and the ligation of dorsal and lateral sacral arteries. In most cases we also made a plastic cast of the distal branches of the aorta, as described by Fuller et al (12). In five studies using radioactive labeled microspheres we verified that at least 95% of the measured blood flow was to the uterus.

3.4 Experiments

3.4.1 Cardiac output and oxygen consumption

Five to six days postoperatively we commenced the experiments. We administered a single dose of 200 mg ketamine intravenously to the ewe before introducing a Swan Ganz flow-directed thermodilution cathether (Edwards Laboratories, 93A-301-7F, Santa Ana, CA) into the right jugular vein. We advanced the tip into the pulmonary artery as shown by the pressure recording during inflation of the balloon (wedging), secured the catheter in position, and allowed a two-hour recovery period before starting the experiments. We measured cardiac output by thermodilution (11), using a cardiac output computer and recorder (with a K-factor, that corrects for catheter volume and injectate volume, of 0.825; Instrumentation Laboratory Inc., Model 601 and 602, Lexington, MA), in triplicate, employing the median value for calculations. In addition, we drew 1 ml blood samples simultaneously from the common internal iliac artery and right atrium, analyzed these in duplicate for oxygen content (Lexington Instruments, Lex O_2 Con-K, Waltham, MA), and used the mean value for calculations.

We exercised the ewe at a room temperature of 22°C for 10-min periods, followed by 20 min of rest. Speed and inclination of the treadmill were gradually increased from initial values of 34 $m.min^{-1}$ at 0 degrees inclination to 99 $m.min^{-1}$ at 10 degrees, until the ewe reached exhaustion within a 10-min exercise period. At this exhaustive level the animal operates at $\dot{V}O_2$ max which we defined as that value when the $\dot{V}O_2$ had plateaued and did not rise further (19). At exhaustion the ewe also panted with open mouth and protruding tongue and showed a staggering gait. Exercise was discontinued if it seemed no longer possible to prevent the animal from collapsing. We made our measurements during the eighth to tenth minute of each exercise period and calculated O_2 consumption according to the Fick principle, from cardiac output and arteriovenous O_2 difference. We measured heart rate from the blood pressure pulse.

3.4.2 Uterine blood flow

One to four days after the preliminary experiment we measured uterine blood flow and vascular pressures. We recorded total uterine blood flow continuously from the flowprobe around the common internal iliac artery. We calibrated the

flowprobes both in vitro and in vivo and found less than 10% error in the factory calibration. Therefore we used the factory calibration in our calculations. We measured flow with an automatic zeroing electromagnetic flowmeter (Dienco, Model RF-2100, Los Angeles, CA) and used a DC amplifier and recorder (Gould Inc., Model 13-4615-10 and 2800, Cleveland, OH). We recorded uterine arterial and venous pressures, using pressure transducers and amplifiers (Gould Inc., Model P23 and 13-4615-50, Cleveland, OH). One minute averages of all variables were calculated by computer (Texas Instruments Inc., Model 990/4, Houston, TX) and stored on disk (Memorex Corp., Markette, Santa Clara, CA).

As illustrated in Figure 2, we studied uterine blood flow during three different exercise regimens: 1) during 10 min of exercise with the treadmill at a speed and inclination similar to that which produced 70% $\dot{V}O_2$ max in the preliminary experiment, followed by 20 min of recovery, 2) during 10 min of exercise at 100% $\dot{V}O_2$ max, which exhausted the ewe, followed by 2 hours of recovery, and 3) during prolonged (40-min) exercise at 70% $\dot{V}O_2$ max, which also exhausted the ewe and was followed by 2 hours of recovery. We calculated 3-min mean values of uterine flow and blood pressures from 2 through 10 min of exercise and 4-min mean values from 2 through 5 min following exercise. We also calculated 5-min means for the control period prior to exercise, from 11 through 40 min of exercise, and from 6 through 60 min following exercise. We repeated one or more of the runs on separate days, up to three times (mean 1.5 times) in each ewe. No systematic difference in response could be demonstrated between subsequent runs at any level tested by two-way analysis of variance. We calculated the mean response to each exercise regimen for each individual animal and used these values for comparison between animals and for statistical analysis.

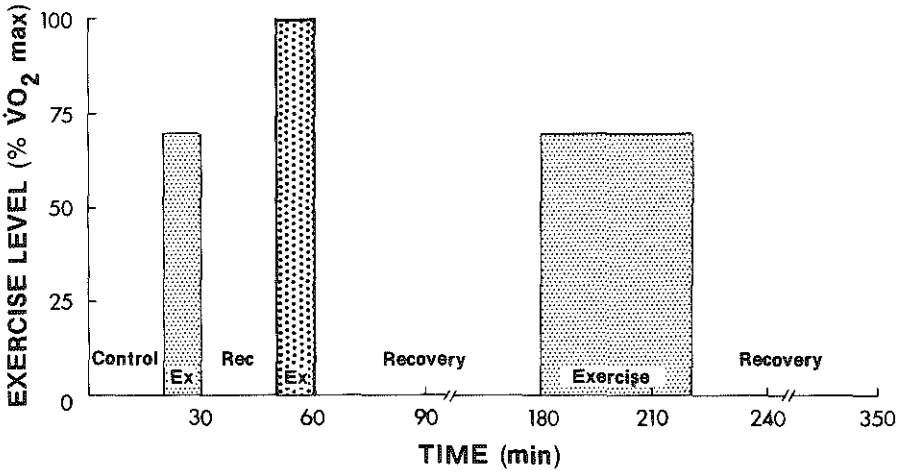

Figure 2. Time course and level of the three different exercise regimens (see text for details).

3.4.3 Blood volume

One to four days after determining the ewe's maximal oxygen consumption and in conjunction with the uterine blood flow studies, we measured blood volumes, using ^{51}Cr labeled erythrocytes (32) in 8 ewes. Eight ml of ^{51}Cr labeled erythrocytes were injected into the maternal circulation 50 min before the beginning of exercise. We obtained arterial samples (2 ml) 30, 20, 10, and 0 min before exercise, 3, 10, 20, 30, and 40 min after the beginning of a single 40-min exercise period at 70% $\dot{V}O_2$ max, and 3, 10, 30, and 60 min after stopping exercise. We counted the samples and injection syringes (before and after injection) for radioactivity in an autogamma scintillation spectrometer (Packard Instruments, Model 5912, Downers Grove, IL) at a 285-357 keV window (peak 323 keV). We used counts from samples taken 30, 20, 10, and 0 min before, and 30 and 60 min after exercise, for linear regression analysis in each animal. We extrapolated the counts to the time of injection by using the same regression for all samples of each individual animal. We measured the microhematocrit of each sample in triplicate and used the median value to calculate plasma and red cell volumes. We measured plasma protein in triplicate, using a refractometer (American Optical Co. TS, Keene, NH), and used median values for comparison.

3.4.4 Statistical analysis

From the control measurements, the experimental measurements and the paired differences between experimental and control values we computed mean values, standard deviations, and standard error of the means for each variable under consideration. We tested differences between means by two-way analysis of variance and Duncan's multiple range test.

4. Results

4.1 Cardiac output and oxygen consumption

Table 1 summarizes the calculated values of heart rate, cardiac output, blood oxygen content, and oxygen consumption at rest and during short-term (10-min) exercise at 70 and 100% $\dot{V}O_2$ max. We normalized cardiac output and oxygen consumption for body weight. Mean maternal weight equaled 55.6 (± 3.8 SEM) kg. Cardiac output increased 170% to 256 (± 27) $ml.min^{-1}.kg^{-1}$ during maximal exercise (Table 1). Arterial oxygen content increased 2.7 (± 0.2) $ml.dl^{-1}$ during maximal exercise, while mixed venous O_2 content decreased 1.3 (± 0.4) $ml.dl^{-1}$, resulting in a 4.1 (± 0.4) $ml.dl^{-1}$ or 110% increase in arteriovenous oxygen content difference. Calculated oxygen consumption increased 5.6 times (range from 3.7 to 7.6 times) from 5.8 (± 0.3) $ml.min^{-1}.kg^{-1}$ at rest to 32.1 (± 2.8) $ml.min^{-1}.kg^{-1}$ (range 18.8 to 57.9 $ml.min^{-1}.kg^{-1}$) during maximal exercise.

Both heart rate and oxygen consumption increased with increasing exercise levels. Figure 3 shows the relationship between heart rate and oxygen consumption,

Table 1. Changes in oxygen consumption and related variables in response to maternal exercise.

	Exercise		Heart rate	Cardiac output	Oxygen content			Oxygen consumption
	Level (% $\dot{V}O_2$ max)	Duration (min)	(bpm)	($ml.min^{-1}.kg^{-1}$)	Arterial ($ml.dl^{-1}$)	Venous ($ml.dl^{-1}$)	A-V ($ml.dl^{-1}$)	($ml.min^{-1}.kg^{-1}$)
control			95 ± 3	149 ± 8	10.5 ± 0.5	6.5 ± 0.4	3.9 ± 0.2	5.8 ± 0.3
exercise	70	10	188 ± 7*	297 ± 20*	12.6 ± 0.4*	5.4 ± 0.4*	7.2 ± 0.2*	21.3 ± 1.6*
exercise	100	10	215 ± 9*†	404 ± 32*†	13.2 ± 0.6*	5.2 ± 0.5*	8.0 ± 0.4*†	32.1 ± 2.8*†

Values are means ± SEM, (n = 13), * $p < 0.01$ compared to control, † $p < 0.01$ compared to previous exercise regimen.

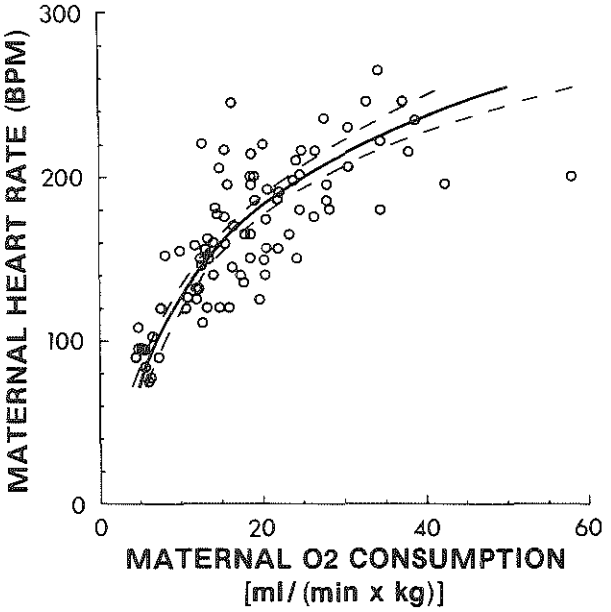

Figure 3. Relation between heart rate and oxygen consumption between 7 and 10 minutes of exercise in near-term pregnant sheep (n = 13). The equation for the line fit by least squares symmetrical regression is y = -56.00 + 79.32 (± 0.0008) ln x.

$y = -56.0 + 79.32\ (\pm\ 0.0008)\ \ln x$ ($R = 0.80$, $p \ll 0.001$), during short-term (10-min) exercise. Heart rate showed a further increase during prolonged exercise, from 188 (± 7) bpm at 8 to 10 min, to 214 (± 16) bpm near the end of 40 min exercise at 70% $\dot{V}O_2$ max.

4.2 Uterine blood flow

During the control period total uterine blood flow averaged 292 (± 26) $ml.min^{-1}.kg\ fetus^{-1}$. We observed considerable spontaneous fluctuations during this period, up to almost 10% of the mean. Table 2 summarizes the changes in uterine blood flow, arterial and venous pressures, and vascular resistance in response to the three different exercise regimens. The values shown in the table represent the 8- to 10-min means during 10-min exercise periods, and the 36- to 40-min means during 40-min exercise periods.

Figure 4 shows the changes in total uterine blood flow during the three different exercise regimens. Uterine blood flow decreased immediately at the onset of exercise and was significantly below control throughout the exercise period. Comparison between the three different exercise regimens showed a larger decrease in uterine blood flow with heavier exercise (100% vs 70% $\dot{V}O_2$ max) and with exercise of longer duration (40 min vs 10 min at 70% $\dot{V}O_2$ max). During a 10-min

Table 2. Changes in uterine blood flow and related variables in response to exercise.

	Exercise		Uterine blood flow	Blood pressure			Uterine vascular resistance
	Level	Duration		uterine A	uterine V	uterine A-V	
	(% $\dot{V}O_2$ max)	(min)	(ml.min^{-1}.kg^{-1}) (n=8)	(mmHg) (n=10)	(mmHg) (n=9)	(mmHg) (n=9)	(mmHg.min.kg.ml^{-1}) (n=7)
control			292 ± 26	87.9 ± 3.3	7.1 ± 1.3	81.5 ± 4.7	0.304 ± 0.031
exercise	70	10	248 ± 13*	102.0 ± 3.7*	8.3 ± 1.9	90.9 ± 7.5*	0.381 ± 0.051*
recovery (20 min)			297 ± 28	87.9 ± 2.4	8.1 ± 1.7	81.1 ± 4.0	0.292 ± 0.029
exercise	100	10	241 ± 13*	104.6 ± 3.4*	8.0 ± 1.6	95.8 ± 4.5*	0.425 ± 0.062*
recovery (20 min)			297 ± 30	85.9 ± 2.0	7.9 ± 1.8	79.7 ± 3.6	0.289 ± 0.022
recovery (120 min)			292 ± 28	83.2 ± 2.6	8.6 ± 1.5	75.1 ± 4.0	0.275 ± 0.027
exercise	70	40	222 ± 19*	100.9 ± 3.3*	8.8 ± 1.7	91.6 ± 4.8*	0.465 ± 0.076*
recovery (20 min)			302 ± 26	85.9 ± 3.4	9.6 ± 1.6	76.1 ± 4.7	0.262 ± 0.036

Values are means ± SEM, * $p < 0.01$ compared to immediate pre-exercise control.

exercise period at 70% $\dot{V}O_2$ max, uterine blood flow decreased 44 (± 16) ml.min^{-1}.kg^{-1}, a 13% drop from its pre-exercise value. During the 10-min exercise period at 100% $\dot{V}O_2$ max we observed a slightly greater decrease in uterine blood flow of 54 (± 16) ml.min^{-1}.kg^{-1}, or 17%. Uterine blood flow showed the most marked decrease, 73 (± 19) ml.min^{-1}.kg^{-1}, or 24%, near the end of 40 min of exercise at 70% $\dot{V}O_2$ max. However, we observed a large variation in uterine blood flow response to exercise among different animals. Near the end of prolonged exercise at 70% $\dot{V}O_2$ max, this change ranged from +4% to −51% of its pre-exercise value.

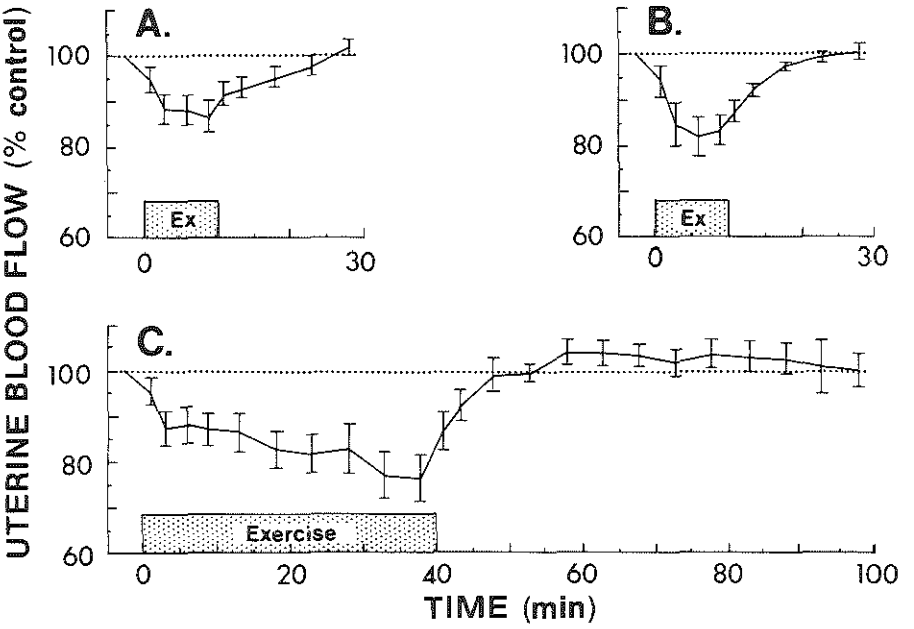

Figure 4. Uterine blood flow response to three different exercise regimens in pregnant sheep (n = 8). Values are means ± SEM. A. 10 min exercise at 70% $\dot{V}O_2$ max, B. 10 min exercise at 100% $\dot{V}O_2$ max, C. 40 min exercise at 70% $\dot{V}O_2$ max.

Although significantly below control, the absolute uterine blood flow values near the end of the three exercise regimens were not significantly different from each other when two-way analysis of variance and Duncan's multiple range test was applied. However, the gradually decreasing uterine blood flow values, as shown in Figure 4C, fit a linear regression and show a highly significant correlation with the duration of exercise ($p < 0.001$). Figure 5 illustrates the inverse linear relationship between total uterine blood flow and maternal heart rate during exercise.

Following the exercise period, uterine blood flow gradually increased, reaching pre-exercise levels within 20 min. After prolonged exercise uterine blood flow demonstrated an insignificant overshoot of 9 (± 7) ml.min^{-1}.kg^{-1} or 4% above resting blood flow.

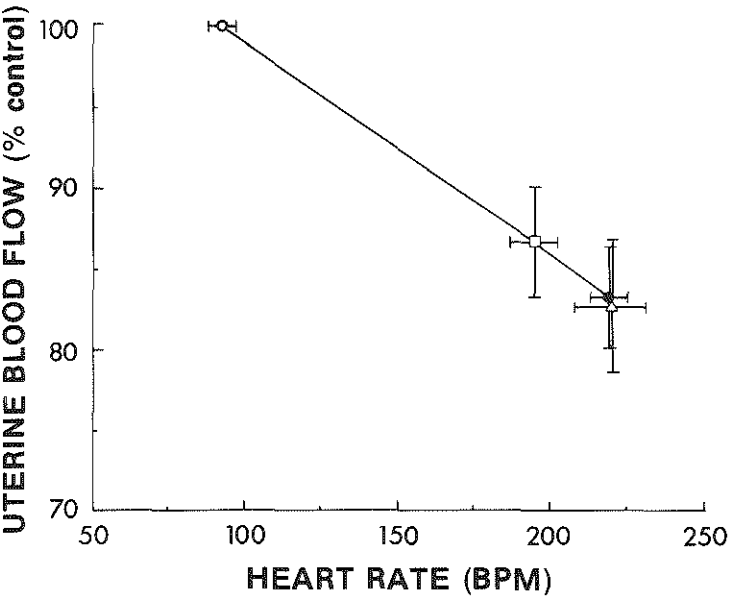

Figure 5. Relation between heart rate and total uterine blood flow in near-term pregnant sheep (n = 8). ○ rest, □ 10 min exercise at 70% $\dot{V}O_2$ max, ● 10 min exercise at 100% $\dot{V}O_2$ max, △ 40 min exercise at 70% $\dot{V}O_2$ max.

Uterine perfusion pressure increased during exercise. This resulted from a rise in arterial pressure, without a change in uterine venous pressure. Although significantly different from control pressures, the perfusion pressures near the end of the three exercise regimens were not significantly different from each other. The calculated uterine vascular resistance increased with the level and the duration of exercise, from 0.275 ± 0.027 mm Hg.min.kg.ml^{-1} at rest to a maximum of 0.465 (± 0.076) mm Hg.min.kg.ml^{-1} (Table 2), a 65% increase from its pre-exercise value.

4.3 Blood volume

Figure 6 summarizes the changes in total blood, plasma and erythrocyte volumes during exercise at 70% $\dot{V}O_2$ max. Red cell volume did not change significantly throughout the period of observation. Within three minutes of the initiation of exercise, whole blood volume decreased 14% from the mean of the four pre-exercise values, from 67.5 (± 3.7) to 57.8 (± 3.6) ml.kg^{-1} ($p < 0.01$). As seen in Figure 6, this resulted from a 20% decrease in plasma volume from 50.9 (± 3.0) to 40.6 (± 3.2) ml.kg^{-1} ($p < 0.01$) while erythrocyte mass remained virtually constant at 16.6 (± 1.2) ml.kg^{-1}. The plasma protein concentration increased only slightly, from 6.2 (± 0.2) to 6.5 (± 0.2) g.dl^{-1}, or 5% of its control value. This change in protein concentration is small compared to the change in plasma volume.

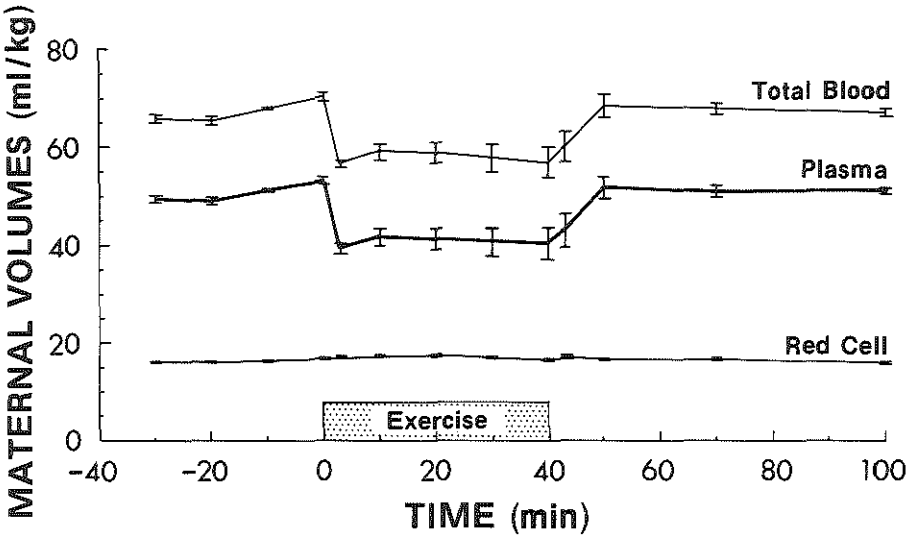

Figure 6. Time course of whole blood, plasma and red cell volumes in relation to 40 min exercise at 70% $\dot{V}O_2$ max in pregnant sheep (n = 8). Values are means ± SEM.

We observed no significant further changes in total blood volume, plasma volume, or protein concentration from 3 to 40 min of exercise. All these variables returned to control values within 10 min following the cessation of exercise.

5. *Discussion*

Several physiologic changes have been studied during exercise in pregnancy, both in humans and laboratory animals. The quantitative significance of most of these studies is limited because they were not done under the most strenuous circumstances (maximal level or prolonged periods of exercise) or because quantification of the exercise stress was poor either in absolute terms (type or duration) or physiologic terms (% $\dot{V}O_2$ max or heart rate).

5.1 Cardiac output and oxygen consumption

Resting O_2 consumption and cardiac output are higher during pregnancy, and $\dot{V}O_2$ increases further during exercise in pregnant women (21) and goats (9). In rats, maximal O_2 consumption, corrected for weight gain during pregnancy, is not different from that of nonpregnant controls (35). Whether or not $\dot{V}O_2$ max is affected by pregnancy has not been studied in other species. Resting O_2 consumption in nonpregnant sheep has been reported to vary from 3.7 to 5.7

ml.min^{-1}.kg^{-1}, values similar to those of humans (1). We found slightly higher values in our pregnant sheep (5.8 ± 0.3 ml.min^{-1}.kg^{-1}). Although this difference could result from differences in methods, breed, and resting "activity", it is likely that resting O_2 consumption, normalized for body weight, is slightly elevated during pregnancy in sheep as it is in humans and goats.

In the present experiments mean maximal O_2 consumption for different ewes was 32.1 (± 2.8) ml.min^{-1}.kg^{-1}, or 5.6 times the resting value (range from 3.7 to 7.6 times control). A similar wide range in physical condition is found in humans (2). Maximal O_2 consumption is relatively unaffected by a variety of moderate stresses (31) and therefore probably was minimally affected by the previous surgery and exercise. In pregnant women $\dot{V}O_2$ max has been calculated from the heart rate response during submaximal exercise to equal 30.8 to 39.5 ml.min^{-1}.kg^{-1} (10, 29). This represents an increase similar to increases we observed in sheep. However, these calculations may be subject to considerable error because the method is only about 85% accurate (2), and the assumption is made that maximal heart rate does not increase as a result of pregnancy, an assumption which has not been tested. We observed considerable differences in maximal heart rate in our pregnant sheep (from 200 to 240 bpm) and demonstrated a correlation between heart rate and oxygen consumption (Fig. 3) similar to that seen in humans (2), except that the mean maximal heart rate in our sheep was sligthly higher (215 bpm) than that seen in humans (@ 200 bpm). This may be the result of pregnancy or of a species difference, and it stresses the need to verify the assumption regarding maximal heart rate in pregnancy.

5.2 Uterine blood flow

Previous studies reported seemingly conflicting results of the uterine blood flow response to exercise. Using the disappearance of ^{24}Na injected into the myometrium, Morris et al (26) suggested a 25% decrease in perfusion of the human pregnant uterus during short-term submaximal bicycle exercise in the supine position. This probably represents an overassessment, since redistribution of blood flow has been shown to occur within the uterus during exercise favoring cotyledonary flow at the cost of myometrial flow (8,18).

In contrast, Orr et al (28) and Curet et al (8) concluded that uterine blood flow in sheep remained constant during treadmill exercise. However, their measurements were made shortly after, rather than during, exercise. In preliminary studies Longo et al (22) showed a decrease of up to 40% in uterine flow during similar exercise in sheep, while Hohimer et al (17) reported only a minimal change in goats. More recently, Hohimer et al (18), Clapp (7), and Chandler and Bell (6) reported decreases in uterine blood flow of up to 36%.

The present data confirm the decrease in uterine flow during exercise, with recovery soon after the exercise is stopped. However, in view of the disagreement as to the magnitude of the effect, it seems appropriate to consider possible errors in uterine blood flow measurements in relation to exercise. Errors in measured uterine

blood flow could result from several factors including 1) technical errors in electromagnetic flowprobe or flowmeter, 2) movement of the flowprobe during exercise which might result in vessel compression, spasm, or stimulation of the sympathetic nerves, 3) excessive catecholamine release prior to, or during, exercise as a result of "stress". (It is unlikely that such stressful factors played an important role in the present study because the animals were accustomed to the treadmill and the laboratory surroundings. However, "other stresses" are an integral part of all exercise experiments involving laboratory animals, and their influence cannot be accurately assessed), 4) other possible problems such as incompletely ligated sacral arteries or formation of collateral vessels resulting in too small a decrease in uterine blood flow, and denervation of the sympathetic nerve supply to the uterine vessels as a result of surgery.

The above mentioned technical errors might explain some of the observed quantitative differences. Variation in the flow responses also might have resulted from the large spontaneous fluctuations in uterine blood flow (as reported by other authors [20, 25, 34] and confirmed in this study) and the differences in the duration and the relative level of exercise.

Our results indicate that uterine blood flow is inversely related to the level and duration of exercise. Uterine blood flow varies inversely with heart rate (Fig. 5) (7, 18), which is directly related to O_2 consumption (Fig. 3). Therefore, uterine blood flow must be inversely related to $\dot{V}O_2$ and the level of exercise, even when the quantitative differences between the three exercise regimens are relatively small in comparison to the baseline variability. The gradual decrease in uterine blood flow with time, as shown in Figure 4C, is highly significant when fitted with a linear regression, which suggests that uterine blood flow decrease is also related to exercise duration.

During exercise we observed increased variability in all measured vascular pressures as a result of changes in the ewe's position relative to the pressure transducers. However, this did not affect the uterine perfusion pressure because a similar variation was seen in both uterine arterial and venous pressures. Perfusion pressure increased from 81.5 ($\pm$ 4.7) mm Hg at rest to a maximum of 95.8 ($\pm$ 4.5) mm Hg during exercise. Calculated uterine vascular resistance increased by a maximum of 65%. This suggests active constriction of the uterine vascular bed.

Decreased uterine blood flow has been associated with hyperthermia (5, 27) and alkalosis (4, 27), both of which occur during exercise. However, the sudden onset of the uterine blood flow changes during exercise (Fig. 4) suggests that the initial large uterine blood flow decrease is not the result of either hyperthermia or alkalosis. Rather, it suggests a neural or hormonal mechanism due to the exercise per se. This could be mediated by sympathetic nerve stimulation or by the systemic release of catecholamines or other vasoactive agents to which the uterine vascular bed is sensitive (15, 16). The further decrease in uterine blood flow with time could result from both hyperthermia and alkalosis.

5.3 Blood volume

To our knowledge no previous measurements of red cell and plasma volumes have been made in any species during exercise in pregnancy. We observed no change in red cell volume. Plasma volume decreased a mean 20% as hematocrit increased from 24.6 (± 1.2)% to 29.6 (± 1.7)% during exercise at 70% $\dot{V}O_2$ max. We observed no further change between 3 and 40 min of exercise, and virtually complete recovery of plasma volume within 10 min after exercise. This is in good agreement with observations in men (13). Chandler and Bell (6) found a slightly smaller change in hematocrit in exercising pregnant sheep. This may be explained by a lower level of exercise, because the magnitude of the plasma volume decrease depends on the level of exercise (13).

The decrease in plasma protein concentration was small, only 24% of the change in plasma volume. This indicates loss of both water and proteins from the intravascular compartment. Greenleaf et al (14) noted in men that both protein and calcium loss during exercise was only half the percentage of plasma volume loss, while sodium, potassium and chloride followed more closely the decrease in plasma volume. He concluded that hydrostatic and/or systemic blood pressures were the major forces driving plasma across the capillary membrane during exercise. However, the rapid response seen in this study suggests a more important role for muscle tissue osmolality changes, as suggested by Lundvall et al (24). One could speculate that the larger decrease in plasma volume and the smaller decrease in plasma proteins during pregnancy, as observed in the present study, could be associated with pregnancy-induced hypervolemia and increased capillary permeability. It is more likely, however, that these differences result from differences in species and methodology. Inherent in the method of calculating plasma and red cell volumes from the microhematocrit is the assumption that the pool of circulating labeled red cells is constant. However, in dogs, red cells sequestered in the spleen are labeled and can be released by catecholamine infusion (3). If labeled red cells are released from the spleen at the onset of exercise the calculated decrease in whole blood and plasma volumes would represent an overestimate. Independent of the cause, the resulting hemoconcentration will help to maintain a relative constant oxygen flow to the pregnant uterus despite exercise-induced reduction in blood flow (23).

6. Significance

We conclude that exercise during pregnancy results in major physiologic changes in the mother, including decreased uterine blood flow and hemoconcentration. The decreased uterine blood flow is a function of the relative workload, which is a function of the level of exercise in physiologic terms (such as % $\dot{V}O_2$ max or heart rate), and its duration. Simultaneously, hemoconcentration will help maintain a relatively constant oxygen delivery to the uterus despite reduction in blood flow.

7. *Acknowledgements*

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CHAPTER THREE

Exercise responses in pregnant sheep: Blood gases, temperatures and fetal cardiovascular system

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1. Abstract

In an effort to examine the effects of maternal exercise on the fetus, we measured maternal and fetal temperatures and blood gases, and calculated uterine O_2 consumption in response to three different treadmill exercise regimens in 12 chronically catheterized near-term sheep. We also measured fetal catecholamine concentrations, heart rate, blood pressure, cardiac output, blood flow distribution, and blood volume, as well as placental diffusing capacity. Maternal and fetal temperatures increased a mean maximum of 1.5 (± 0.5 SEM) and 1.3 (± 0.1) °C, respectively. We corrected maternal and fetal blood gas values for the temperatures in vivo. Near exhaustion during prolonged (40-min) exercise at 70% $\dot{V}O_2$ max, maternal arterial P_{O_2} increased 13% to a maximum of 116.7 (± 4.0) Torr, while P_{CO_2} decreased 28% to 27.6 (± 2.2) Torr. Fetal arterial P_{O_2} decreased 11% to a minimum of 23.2 (± 1.6) Torr; O_2 content 26% to 4.3 (± 0.6) ml.dl^{-1}; and P_{CO_2} 8% to 49.6 (± 3.2) Torr, while pH did not change significantly. Recovery was virtually complete within 20 min. During exercise total uterine O_2 consumption was maintained despite the reduction in uterine blood flow, because of hemoconcentration and increased O_2 extraction. The decrease of 3 Torr in fetal arterial O_2 tension and 1.5 ml.dl^{-1} in O_2 content did not result in major cardiovascular changes or catecholamine release. These findings suggest that maternal exercise does not represent a major stressful or hypoxic event to the fetus.

2. *Introduction*

Both pregnancy and exercise are associated with physiologic changes in the maternal cardiovascular system, such as increases in oxygen consumption (2, 38), heart rate, and cardiac output (2, 31). Acute exercise is also associated with a redistribution of blood flow from the splanchnic bed to the exercising muscles (11). Recently we have shown (26) that during exercise blood flow to the pregnant uterus decreases, the magnitude of which seems to depend upon the maternal physical condition ($\dot{V}O_2$ max) and the workload. During pregnancy the continuous delivery of oxygen and other substrates is essential for fetal well-being. Therefore, maternal exercise with reduced uterine blood flow could stress the fetus. However, we also noted maternal hemoconcentration during exercise, which increases the blood O_2 carrying capacity and may protect the fetus from hypoxia.

Previous studies in pregnant sheep (8, 10, 14, 24) reported decreases of 18 to 29% in fetal arterial oxygen tension and content during maternal exercise. The reported decreases in uterine blood flow (up to 40%) probably cannot fully explain these changes, as fetal O_2 tension is maintained when uterine blood flow is 60% or more of its normal resting value (21). None of the above mentioned studies corrected for the exercise induced changes in maternal and fetal body temperature. Blood obtained anaerobically and analyzed for blood gases at a temperature below that of the body shows a rise in pH and a fall in O_2 and CO_2 tensions (34). Thus, consideration of exercise induced temperature changes is essential for a correct assessment of the changes in respiratory blood gases in vivo. Also, if placental CO diffusing capacity were acutely decreased during maternal exercise, this could explain the changes in fetal blood gases.

Acute fetal hypoxia is associated with release of catecholamines (12), and changes in heart rate, blood pressure (6), blood flow distribution (23), and hematocrit (35). Absence of any such changes would suggest that maternal exercise does not represent a major hypoxic stress to the fetus.

In an effort to determine whether or not fetal homeostasis is maintained during exercise, we measured maternal and fetal temperatures, blood gases, and carbohydrate concentrations and calculated uterine oxygen consumption. To explore other possible fetal and placental responses to maternal exercise, we measured fetal catecholamine concentrations, heart rate, blood pressure, cardiac output, blood flow distribution and blood volume, as well as placental diffusing capacity for CO.

3. *Methods*

3.1 *Principle of Method*

In a preliminary experiment we determined maximal oxygen consumption ($\dot{V}O_2$ max) in each ewe (26). One to five days later we measured maternal and fetal temperatures, respiratory blood gases, and carbohydrate concentrations, as well as

fetal catecholamine concentrations, heart rate, arterial pressure, cardiac output, blood flow distribution, and blood volume in sheep in response to three different treadmill exercise regimens: 1) 10 min exercise at 70% $\dot{V}O_2$ max, 2) 10 min at 100% $\dot{V}O_2$ max, and 3) 40 min at 70% $\dot{V}O_2$ max.

3.2 Animals

We studied 12 ewes of mixed western breed with singleton pregnancy, from 117 to 135 days (term 147 days). All animals appeared healthy and had normal blood gases at the time of the experiments. We conditioned the ewes to walk on the treadmill at various speeds for short intermittent periods, totaling 10 min each day, for 1 week prior to surgery. During this time the ewes were fed alfalfa pellets ad libitum. Twelve to twenty-four hours prior to surgery the animals were taken off food, but water remained available.

3.3 Surgery

We performed surgery in two phases, using spinal anesthesia supplemented with pentobarbital. In the first phase we used a midline abdominal incision to expose the uterus. Through a hysterotomy incision we inserted catheters into the fetal ascending and descending aortae and superior and inferior vena cavae via vessels in the fore- and hindlimbs. We placed catheters in the amniotic fluid and in the uterine vein of the pregnant horn and closed the uterus. In the last six animals we placed a thermistor in the fetal inferior vena cava as well as in a small distal branch of the uterine artery. We closed the abdominal fascia and passed the catheters subcutaneously through a stab wound in the left flank into a nylon pouch attached to the skin for protection.

Immediately following the first phase of surgery we placed the ewe in the right lateral position for a retroperitoneal approach to the distal branches of the aorta. We introduced a Tygon catheter (1.5 mm od) into the left lateral sacral artery for pressure recording and blood sampling. We ligated the lateral and dorsal sacral arteries and placed an electromagnetic flowprobe around the common internal iliac artery to measure uterine blood flow, as described previously (26).

We flushed the catheters each day with 2 ml saline containing 1 unit of heparin per ml, injected 500 mg of Ampicillin into the amniotic fluid, and administered 2 ml of Combiotic intramuscularly to the ewe.

3.4 Preliminary experiment

Five to six days postoperatively we commenced the experiments. We measured maximal oxygen consumption and determined the speed and inclination of the treadmill which produced 70% and 100% $\dot{V}O_2$ max in each individual ewe (26).

3.5 Temperatures

In the first six animals we measured maternal rectal temperatures at rest and during exercise (Yellow Springs Instruments Co., Telethermometer, Yellow Springs, OH) without measuring fetal body temperatures. In the following six animals we measured maternal and fetal temperatures continuously, using thermistors (Instrumentation Laboratory Inc., model 601, Lexington, MA) and DC amplifier and recorder (Gould Inc., model 13-4615-10 and 2800, Cleveland, OH). The thermistors were calibrated before implantation and after removal and found to vary by less than 0.02°C.

3.6 Respiratory blood gases

We measured maternal and fetal respiratory blood gases at rest, during the three exercise regimens (10 min at 70% $\dot{V}O_2$ max, 10 min at 100% $\dot{V}O_2$ max, 40 min at 70% $\dot{V}O_2$ max), and during recovery, following the protocol previously described (26). We obtained 1 ml samples from the uterine artery and vein and the fetal ascending aorta, 1 to 3 minutes before the beginning and end of each exercise period, and 18 to 20 min and 116 to 120 min following the cessation of exercise. We measured PO_2, PCO_2, and pH (Radiometer, model ABL2, Copenhagen) at 37°C. We corrected the maternal values for the body temperature, as measured by rectal probe in the first six animals and by uterine artery thermistor in the latter six ewes. Similarly we corrected the blood gas values in the latter six fetuses for the temperatures, as measured by the fetal thermistor. From the maternal and fetal temperatures, as measured in the latter six animals, we calculated fetal-maternal temperature differences at each level of exercise. Assuming similar gradients at similar levels of exercise in the first six animals, we individually corrected the measured blood gas values in the first six fetuses. We used the following formulae, modified after Severinghaus (34), to correct maternal and fetal values for the anaerobic temperature changes:

$$pH\ (t°C) = pH\ (37°) - 0.0147\ (t - 37) \quad (1)$$

$$PO_2\ (t°C) = PO_2\ (37°C) \cdot 10^{0.031(t-37)} \text{ if } 0 < PO_2 \leqslant 72 \quad (2)$$

$$PCO_2\ (t°C) = PCO_2\ (37°C) \cdot 10^{0.021(t-37)} \quad (3)$$

We measured O_2 content in duplicate (Lexington Instruments, LexO_2Con-K, Waltham, MA) and calculated mean values. Differences between duplicate measurements were within 0.2 ml.dl^{-1}. We calculated uterine O_2 consumption from the uterine arteriovenous O_2 content difference and the simultaneously measured total uterine blood flow. (See ref. 26 for details of the uterine blood flow measurements).

3.7 Glucose, lactate and pyruvate

We measured maternal and fetal arterial glucose, lactate, and pyruvate concentrations in 8 animals in a single experiment, following the same protocol as for blood gases. We rapidly and anaerobically sampled the blood (2.5 ml), using iced, heparinized syringes. Immediately we pipetted 2 ml of blood into 4 ml cold 8% perchloric acid to precipitate plasma proteins. After centrifugation the samples were stored at 0°C for assay within one week. We measured pyruvic acid and lactic acid spectrophotometrically at 340 mm (Hitachi, model 100-20, Tokyo, Japan), using a standard assay (Sigma, No. 726-UV and 826-UV, St. Louis, MO). We used 0.5 ml samples for glucose analysis (Beckman Instruments Inc., model Astra-8, Brea, CA).

3.8 Placental diffusing capacity for carbon monoxide

We measured placental diffusing capacity for carbon monoxide (22) in 5 animals. The ewe breathed a loading dose of 125 ml CO in 10 l room air for 1.5 min. Thereafter she breathed for 70 min a mixture of 100 ppm CO in air. This was supplied at a flow of 30 $l.min^{-1}$ into a movable plastic bag fitted around the head and neck. We monitored the inspired CO concentration with a CO analyzer (Energetic Science Inc., Ecolyzer, Elmsford, NY). With the ewe standing quietly on the treadmill, we collected samples (1.5 ml) simultaneously from the uterine vein and fetal aorta 10, 25, and 40 min following the start of CO administration. Thereafter we exercised the ewe for 30 min at 70% $\dot{V}O_2$ max and collected samples 15 and 30 min following the start of exercise. We calculated a mean placental diffusing capacity for the 30 min periods prior to, and during, exercise.

3.9 Catecholamines

We sampled arterial blood (1.5 ml) for catecholamine concentrations in 10 fetuses. Samples were taken at rest, during the 8th min of exercise at 70 and 100% $\dot{V}O_2$ max, during the 38th min of exercise at 70% $\dot{V}O_2$ max, and 18 min after cessation of each exercise regimen. We stored the samples on ice immediately upon drawing. After centrifugation 500 μl plasma was added to 15 μl of 70% perchloric acid to precipitate plasma proteins. The plasma was stored at –70°C until assayed within 6 months. We measured plasma epinephrine, norepinephrine, and dopamine concentrations, utilizing a catechol-O-methyltransferase radioenzymatic assay, and using the methods of Pauler and Johnson (30), as modified by Roizen et al (32). The sensitivity of the assays was 50, 100, and 150 $pg.ml^{-1}$ for epinephrine, norepinephrine, and dopamine, respectively.

3.10 Heart rate and arterial pressure

We recorded fetal aortic pressure and amniotic fluid pressure in 12 animals, using

pressure transducers and amplifiers (Gould Inc., Model P23 and 13-4615-50, Cleveland, OH), and corrected the fetal arterial pressure for amniotic fluid pressure.

3.11 Cardiac output and blood flow distribution

We measured cardiac output and blood flow distribution in 6 fetuses, using microspheres 15(±1) micron in diameter labeled with ^{46}Sc, ^{51}Cr, ^{103}Ru, or ^{153}Gd (New England Nuclear Co., Boston, MA), as previously described (23). Injections were made at rest, during the last 3 min of 10 min of exercise at 70 and 100% $\dot{V}O_2$ max and 40 min of exercise at 70% $\dot{V}O_2$ max. We sacrificed the ewe and fetus zero to two days following the experiment, using 20 ml Euthanol solution (National Laboratories Corp., Summerville, NJ). Fetal organs as well as placental cotyledons and membranes were weighed, ashed, and counted for radioactivity. We calculated absolute organ blood flow per kilogram fetus and the percentage of cardiac output distributed to the different organs.

3.12 Blood volume

We measured blood volume, hematocrit, and plasma protein concentration in 8 fetuses and calculated plasma and red cell volumes, as previously described (26).

3.13 Statistical analysis

For all continuously measured variables we calculated one-min averages (Texas Instruments Inc., model 990/4, Houston, TX) and stored the data on disk (Memorex Corp., Markette, Santa Clara, CA). We calculated 3-min mean values from 2 through 10 min of exercise and 4-min mean values from 2 through 5 min following exercise. In addition, we calculated 5-min mean values during the control period prior to exercise, from 11 through 40 min of exercise, and from 5 through 60 min following exercise. We repeated one or more of the three different exercise regimens, up to four times (mean 1.9 times) in each ewe. For neither the continuously measured variables nor the blood gases could we demonstrate a systematic difference in response between subsequent runs at any level tested by two-way analysis of variance. We calculated the mean response to each exercise regimen for each individual animal and used these values for comparison between animals and for statistical analysis.

From the control measurements, the experimental measurements, and the paired differences between experimental and control values we computed mean values, standard deviations, and standard error of the means for each variable under consideration. We tested differences between means by two-way analysis of variance and Duncan's multiple range test.

4. Results

4.1 Temperatures

The changes in maternal and fetal temperatures during exercise, as measured with thermistors in 6 animals, are shown in Figure 1. We found no significant difference between the mean rectal temperature in the first six ewes and the uterine artery temperature in the latter six ewes at rest or during exercise or recovery. Therefore we combined the results of all 12 animals (Table 1). Mean maternal temperature was 39.2 (± 0.1) °C at rest, increasing rapidly at the onset of exercise by 0.8 (± 0.2)°C after 8 to 10 min of exercise at 70% $\dot{V}O_2$ max, 1.3 (± 0.1) °C after 8 to 10 min at 100% $\dot{V}O_2$ max, and 1.5 (± 0.2)°C after 36 to 40 min of exercise at 70% $\dot{V}O_2$ max. When the exercise was discontinued, maternal temperature initially fell rapidly but remained elevated for more than one hour after 40 min exercise at 70% $\dot{V}O_2$ max.

Fetal temperature averaged 39.6 (± 0.1)°C at rest. During the first few minutes of exercise fetal temperature increased more slowly than did the maternal. This resulted in a reduction or even reversal of the normal fetal-maternal temperature

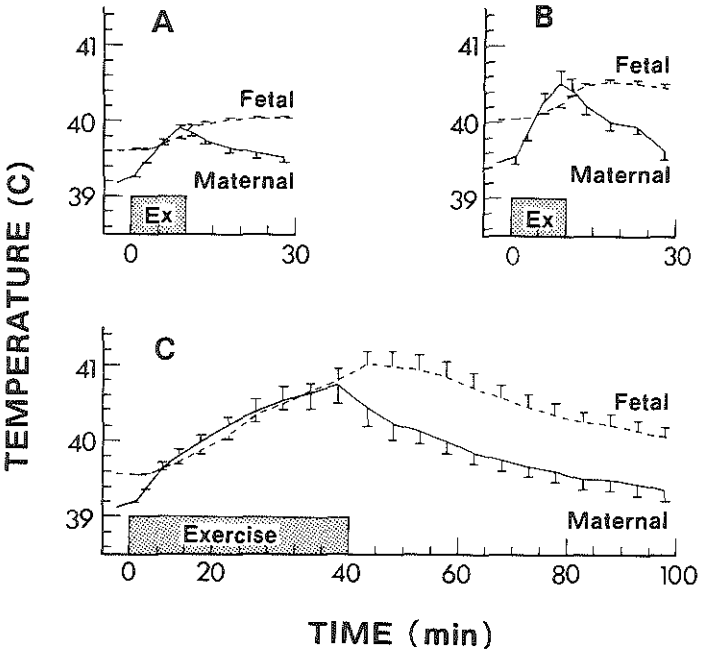

Figure 1. Maternal and fetal temperature changes in response to three different exercise regimens. Values are means ± SEM (n = 6). A. 10 min exercise at 70% $\dot{V}O_2$ max, B. 10 min exercise at 100% $\dot{V}O_2$ max, C. 40 min exercise at 70% $\dot{V}O_2$ max.

gradient (Fig. 1 and Table 1). Near the end of 40 min of exercise at 70% $\dot{V}O_2$ max, fetal temperature was 1.3 (± 0.1)°C higher than at rest. During the first few minutes following the cessation of exercise, fetal temperature showed a slight, but insignificant, further increase. Thereafter fetal temperature decreased more slowly than the maternal temperature. Soon after cessation of 40 min of exercise at 70% $\dot{V}O_2$ max, the fetal-maternal temperature gradient had increased to about 0.7°C. After one hour recovery fetal temperatures were still significantly increased.

4.2 Respiratory blood gases

Table 1 shows the exercise associated changes in blood gases. Two-way analysis of variance did not show significant differences in blood gas values between the first six ewes and their fetuses and the latter six animals at rest, or during exercise or recovery. Therefore we combined the results of all 12 animals.

Maternal arterial O_2 tension, O_2 content, and pH increased with exercise, while CO_2 tension decreased. Although significantly different from control values, O_2 tension and content were not different among the three exercise regimens. CO_2 tension and pH were significantly different from control during all three exercise regimens, and the values near the end of prolonged exercise (40-min) at 70% $\dot{V}O_2$ max were significantly lower than during short-term exercise. Maternal O_2 tension increased maximally 13.1 (± 0.4) Torr from a mean 103.6 (± 2.6) Torr at rest and O_2 content increased maximally 2.7 (± 0.4) ml.dl^{-1} from 10.6 (± 0.6) ml.dl^{-1} at rest, while CO_2 tension decreased 10.8 (± 1.7) Torr during prolonged exercise from 38.3 (± 1.0) Torr at rest and pH increased 0.11 from 7.45 (± 0.01) units at rest. Figure 2 shows the percent changes. With the exception of PCO_2 following prolonged exercise, all maternal blood gas values returned to control values within 20 min of recovery.

Mean fetal arterial oxygen tension, oxygen content, and carbon dioxide tension decreased with increasing level and duration of exercise, while pH increased. However, the changes in fetal blood gases differed significantly from control values only when the ewes were run to exhaustion. Near the end of 40 min exercise at 70% $\dot{V}O_2$ max, O_2 tension decreased 3.0 (± 0.8) Torr, to 23.2 (± 1.6) Torr, from a value of 26.2 (± 1.6) Torr at rest, arterial oxygen content decreased 1.5 (± 0.2) ml.dl^{-1} from 5.8 (± 0.7) ml.dl^{-1} at rest, and CO_2 tension decreased 4.5 (± 1.9) Torr from 54.1 (± 1.7) Torr at rest, while the pH increased 0.02 (± 0.02) units. The percent changes are shown in Figure 2. With the exception of oxygen content, all fetal blood gases returned to control values within 20 min from cessation of exercise. None of the fetuses died during or following the exercise period.

Table 1. Changes in temperature and arterial respiratory gas

	exercise				maternal
	level ($\%\dot{V}O_2$ max)	duration (min)	temp (°C)	pH	P_{CO_2} (Torr)
			(n=12)	(n=12)	(n=12)
control			39.2 ± 0.1	7.45 ± 0.01	39.7 ± 1.3
exercise	70	10	40.1 ± 0.2*	7.48 ± 0.01*	35.0 ± 1.5*
recovery (20 min)			39.3 ± 0.1	7.45 ± 0.01	36.6 ± 0.6
exercise	100	10	40.7 ± 0.1*†	7.48 ± 0.01*	33.8 ± 1.4*
recovery (20 min)			39.5 ± 0.1	7.44 ± 0.01	37.3 ± 0.9
recovery (120 min)			39.1 ± 0.1	7.45 ± 0.01	38.3 ± 1.0
exercise	70	40	40.6 ± 0.2*†	7.56 ± 0.02*†	27.6 ± 2.2*†
recovery (20 min)			39.9 ± 0.2*†	7.46 ± 0.01	35.0 ± 1.2*†

Values are means ± SEM * $p < 0.01$ compared to immediate pre-exercise control, † $p < 0.01$ compared to previous exercise

4.3 Uterine oxygen consumption

Table 2 shows the changes in total uterine blood flow, oxygen delivery, arteriovenous oxygen content difference, and oxygen consumption.

During short-term exercise at 70% $\dot{V}O_2$ max the decrease in uterine blood flow (7%) was proportionally less than the increase in arterial oxygen content (26%), resulting in slightly increased (11%, N.S.) O_2 delivery to the pregnant uterus, but uterine oxygen consumption did not change significantly. During 10 min of exercise at 100% $\dot{V}O_2$ max, uterine blood flow decreased 13% to 268 (± 19) $ml.min^{-1}.kg\ fetus^{-1}$, while arterial O_2 content increased 24% to 13.2 (± 0.6) $ml.dl^{-1}$. Oxygen delivery to the uterus increased slightly to 35.3 (± 3.3) from 28.6 (± 3.2) $ml.min^{-1}.kg\ fetus^{-1}$ (N.S.). Uterine oxygen consumption increased also slightly to 9.9 (± 0.9) from 8.3 (± 1.3) $ml.min^{-1}.kg\ fetus^{-1}$ (N.S.).

Near the end of prolonged (40 min) exercise at 70% $\dot{V}O_2$ max, with the ewes near exhaustion, uterine blood flow decreased 29% to 219 (± 32) $ml.min^{-1}.kg^{-1}$. This decrease was proportionally greater than the increase in arterial oxygen content (25%), to 13.3 (± 0.9) $ml.dl^{-1}$, resulting in an 11% decrease (N.S.) in oxygen delivery to the uterus. As a result of significantly increased oxygen extraction by the uterus (22%), as shown by the widening arteriovenous oxygen content difference to 4.1 (± 0.9) $ml.dl^{-1}$ from 3.0 (± 0.4) $ml.dl^{-1}$, uterine oxygen consumption was not different from the pre-exercise value, 7.9 (± 0.8) and 7.6 (± 1.0) $ml.min^{-1}.kg^{-1}$, respectively. All of the above variables returned to control values within 20 min of recovery.

levels in mother and fetus in response to maternal exercise.

		fetal				
P_{O_2} (Torr)	$[O_2]$ (ml.dl^{-1})	temp (°C)	pH	P_{CO_2} (Torr)	P_{O_2} (Torr)	$[O_2]$ (ml.dl^{-1})
(n=12)	(n=12)	(n=6)	(n=12)	(n=12)	(n=12)	(n=12)
105.1 ± 1.6	10.6 ± 0.5	39.6 ± 0.9	7.33 ± 0.00	55.1 ± 1.5	26.1 ± 1.2	6.2 ± 0.5
113.7 ± 3.1*	12.8 ± 0.5*	40.0 ± 0.1*	7.36 ± 0.01	52.4 ± 1.9	25.2 ± 1.2	5.9 ± 0.5
106.4 ± 3.2	10.9 ± 0.5	39.9 ± 0.1*	7.32 ± 0.01	55.1 ± 2.1	24.7 ± 1.7	5.8 ± 0.8
114.7 ± 2.0*	13.2 ± 0.6*	40.3 ± 0.1*†	7.35 ± 0.01*	52.2 ± 1.9*	24.8 ± 1.3	5.4 ± 0.5
102.2 ± 2.0	10.7 ± 0.4	40.4 ± 0.1*†	7.33 ± 0.01	53.6 ± 1.7	25.8 ± 1.4	5.5 ± 0.6
103.6 ± 2.6	10.6 ± 0.6	39.5 ± 0.1	7.32 ± 0.01	54.1 ± 1.7	26.2 ± 1.6	5.8 ± 0.7
116.7 ± 4.0*	13.3 ± 0.9*	40.8 ± 0.1*†	7.34 ± 0.03	49.6 ± 3.2*	23.2 ± 1.6*†	4.3 ± 0.6*†
103.5 ± 1.6	10.8 ± 0.7	40.7 ± 0.2*†	7.31 ± 0.03	51.8 ± 2.7	25.7 ± 1.8	4.8 ± 0.6*†

regimen.

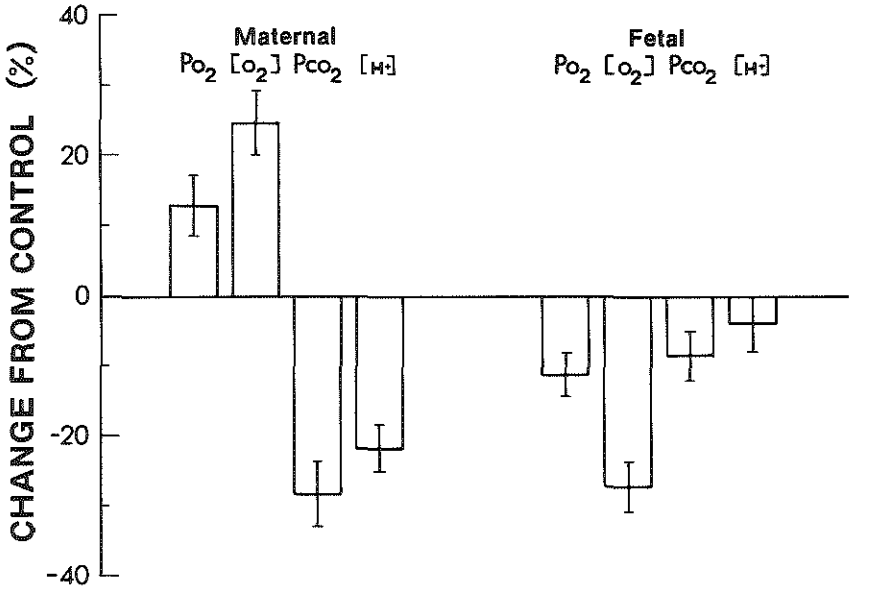

Figure 2. Percent changes in maternal and fetal respiratory blood gas concentrations during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. Values are means ± SEM (n = 12).

Table 2. Changes in uterine oxygen consumption and related variables in response to maternal exercise.

	exercise		uterine blood flow	O_2 content			uterine O_2 delivery	uterine O_2 extraction	uterine O_2 consumption
	level	duration		ut A	ut V	ut A-V			
	(%$\dot{V}O_2$ max)	(min)	($ml.min^{-1}.kg^{-1}$)	($ml.dl^{-1}$)	($ml.dl^{-1}$)	($ml.dl^{-1}$)	($ml.min^{-1}.kg^{-1}$)	($ml.min^{-1}.kg^{-1}$)	($ml.min^{-1}.kg^{-1}$)
			(n=8)	(n=12)	(n=10)	(n=10)	(n=10)	(n=10)	(n=8)
control			301 ± 23	10.6 ± 0.5	7.6 ± 0.5	2.7 ± 0.3	31.7 ± 3.7	0.26 ± 0.03	7.8 ± 1.1
exercise	70	10	278 ± 20*	12.8 ± 0.5*	9.1 ± 0.5*	3.3 ± 0.3	35.7 ± 3.7	0.27 ± 0.03	8.8 ± 0.9
recovery (20 min)			274 ± 18	10.9 ± 0.5	8.1 ± 0.9	3.0 ± 0.3	28.0 ± 3.2	0.28 ± 0.04	8.3 ± 1.3
exercise	100	10	268 ± 19*	13.2 ± 0.6*	9.1 ± 0.6*	3.6 ± 0.3*	35.3 ± 3.3	0.29 ± 0.02	9.9 ± 0.9
recovery (20 min)			294 ± 31	10.7 ± 0.4	8.1 ± 0.8	3.0 ± 0.3	33.2 ± 5.4	0.28 ± 0.04	8.3 ± 1.0
recovery (120 min)			315 ± 51	10.6 ± 0.6	8.1 ± 1.1	3.0 ± 0.4	34.2 ± 7.2	0.28 ± 0.05	7.6 ± 1.0
exercise	70	40	219 ± 32*	13.3 ± 0.9*	8.8 ± 1.1*	4.1 ± 0.9*†	30.5 ± 6.6	0.31 ± 0.05*†	7.9 ± 0.8
recovery (20 min)			326 ± 58	10.8 ± 0.7	7.7 ± 0.9	2.9 ± 0.4	36.4 ± 7.8	0.27 ± 0.03	7.9 ± 1.0

Values are means ± SEM, * $p < 0.01$ compared to immediate pre-exercise control, † $p < 0.01$ compared to previous exercise regimen.

4.4 Glucose, lactate and pyruvate

The exercise associated changes in carbohydrate concentrations are shown in Table 3. Maternal arterial glucose, lactate, and pyruvate concentrations all increased with the level and the duration of exercise. Glucose increased from a control value of 60.7 (± 5.7) mg.dl^{-1} to a maximum of 82.1 (± 7.2) mg.dl^{-1} after 36 to 40 min of exercise at 70% $\dot{V}O_2$ max, while lactate increased from 1.20 (± 0.24) to 4.56 (± 0.76) mg.dl^{-1} and pyruvate from 0.07 (± 0.02) to 0.27 (± 0.03) mg.dl^{-1}. The lactate-pyruvate ratio did not change significantly. After 20 min of recovery glucose, lactate, and pyruvate concentrations were still above control values.

Fetal lactate concentrations increased from 1.54 (± 0.35) mg.dl^{-1} to a maximum of 2.59 (± 0.82) mg.dl^{-1} during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max, while the changes in glucose and pyruvate concentrations were not significant. As a result the lactate-pyruvate ratio increased from 22.9 (± 8.8) to 31.3 (± 12.5) ($p < 0.05$). After 20 min of recovery fetal lactate concentrations still exceeded control values.

4.5 Placental diffusing capacity

Placental diffusing capacity for carbon monoxide equaled 0.400 (± 0.033) ml.min^{-1}.Torr^{-1}.kg fetus^{-1} at rest and 0.394 (± 0.035) ml.min^{-1}.Torr^{-1}.kg^{-1} during exercise at 70% $\dot{V}O_2$ max. The difference was insignificant.

4.6 Catecholamines

Epinephrine and dopamine concentrations were below the sensitivity of the assay (50 and 150 pg.ml^{-1}, respectively) throughout most of the experiment in 8 out of 10 fetuses. Norepinephrine concentrations were above the sensitivity of the assay (100 pg.ml^{-1}) in most fetuses. We observed considerable variation in norepinephrine values at rest (93 to 366 pg.ml^{-1}), during exercise (24 to 1322 pg.ml^{-}), and during recovery (61 to 1262 pg.ml^{-1}). Although the mean norepinephrine concentration increased with the level and the duration of exercise – from 212 (± 36) pg.ml^{-1} at rest to 309 (± 86) pg.ml^{-1} during 10 min of exercise at 70% $\dot{V}O_2$ max; 430 (± 176) pg.ml^{-1} during 10 min of exercise at 100% $\dot{V}O_2$ max; and 424 (± 152) pg.ml^{-1} during 40 min of exercise at 70% $\dot{V}O_2$ max – the changes during exercise and recovery were not significant.

4.7 Heart rate and arterial pressure

We found no significant changes in fetal heart rate or arterial blood pressure in response to exercise. Resting heart rate and arterial pressure were 156 (± 10) bpm and 45.4 (± 3.1) mm Hg respectively. After 36 to 40 min of exercise at 70% $\dot{V}O_2$ max, fetal heart rate was 158 (± 8) bpm and arterial pressure 46.0 (± 3.6) mm Hg.

Table 3. Changes in maternal and fetal arterial carbohydrate concentrations in response to maternal exercise.

	exercise		maternal				fetal			
	level ($\%\dot{V}O_2$ max)	duration (min)	glucose ($mg.dl^{-1}$)	lactate ($ml.dl^{-1}$)	pyruvate ($mg.dl^{-1}$)	L/P	glucose ($mg.dl^{-1}$)	lactate ($mg.dl^{-1}$)	pyruvate ($mg.dl^{-1}$)	L/P
			(n=7)	(n=9)	(n=9)	(n=9)	(n=7)	(n=7)	(n=9)	(n=7)
control			54.3 ± 3.5	0.83 ± 0.13	0.07 ± 0.02	14.6 ± 1.5	14.0 ± 3.5	1.47 ± 0.31	0.18 ± 0.04	15.8 ± 3.9
exercise	70	10	64.3 ± 2.8	2.26 ± 0.32*	0.17 ± 0.02*	15.5 ± 1.7	14.3 ± 2.9	1.61 ± 0.33	0.20 ± 0.04	17.1 ± 5.1
recovery (20 min)			62.9 ± 4.0	1.40 ± 0.12	0.10 ± 0.02	16.5 ± 2.4	16.1 ± 2.4	1.59 ± 0.31	0.16 ± 0.04	20.2 ± 5.0
exercise	100	10	69.2 ± 4.1	2.64 ± 0.42*	0.23 ± 0.03*†	13.2 ± 2.1	16.3 ± 3.2	1.64 ± 0.32	0.16 ± 0.04	22.0 ± 5.6
recovery (20 min)			69.9 ± 4.6	2.00 ± 0.26	0.11 ± 0.02	28.1 ± 9.9	19.7 ± 3.2	1.67 ± 0.37	0.17 ± 0.04	21.2 ± 5.6
recovery (120 min)			60.7 ± 5.7	1.20 ± 0.24	0.07 ± 0.02	28.7 ± 13.5	11.0 ± 2.2	1.54 ± 0.35	0.17 ± 0.04	22.9 ± 8.8
exercise	70	40	82.1 ± 7.2*†	4.56 ± 0.76*†	0.27 ± 0.03*	18.0 ± 3.0	17.4 ± 3.5	2.59 ± 0.82*†	0.17 ± 0.03	31.3 ± 12.5
recovery (20 min)			76.9 ± 5.0*†	3.20 ± 0.65*†	0.15 ± 0.02*	25.1 ± 6.7	17.0 ± 3.1	2.57 ± 0.76*†	0.18 ± 0.04	17.4 ± 5.6

Values are means ± SEM, * $p < 0.01$ compared to immediate pre-exercise control, † $p < 0.01$ compared to previous exercise regimen.

4.8 Cardiac output and blood flow distribution

Control cardiac output equaled 434 (± 36) $ml.min^{-1}.kg\ fetus^{-1}$. Blood flow distribution to the placenta and the various fetal organs was normal [placenta 36 (± 1)%, brain 7 (± 0)%, heart 6 (± 2)%, kidney 2 (± 0)%, gastro-intestinal tract 7 (± 0)%]. We observed no significant changes in cardiac output, absolute organ blood flow, or cardiac output distribution during short-term (10 min) exercise at 70% and 100% $\dot{V}O_2$ max, in 6 fetuses. In only two fetuses did we obtain adequate withdrawals during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. This number is too low to allow any conclusions on the effects of prolonged exercise.

4.9 Blood volume

We observed no changes in fetal total blood, plasma, and red cell volumes or in plasma protein concentration during and following 40 min of exercise at 70% $\dot{V}O_2$ max. Mean resting total blood volume, plasma volume, and red cell volumes equaled 120 (± 7), 80 (± 5), and 40 (± 4) $ml.kg^{-1}$ respectively, and the mean resting plasma protein concentration equaled 3.6 (± 0.1) $g.dl^{-1}$.

5. Discussion

5.1 Temperatures

Changes in maternal and fetal body temperatures have not previously been studied during exercise. Under resting conditions fetal temperature exceeds that of the mother by about 0.5°C as a result of the higher rate of fetal metabolism and the requirement of heat to dissipate to the mother (1).

The data from our last six animals demonstrate considerable temperature increases during exercise (Fig. 1), indicating that a constant fetal-maternal temperature gradient of 0.5°C does not persist under these conditions. These data are in good agreement with a recently proposed mathematical model of fetal-maternal heat exchange by Schröder et al (33). This model assumes that under steady state conditions 80% of the heat diffuses across the placenta, while 20% exchanges across the fetal skin, amniotic fluid, and uterine wall, with a fetal skin conductance of 164 $cal.min^{-1}.°C^{-1}$ and a uterine wall conductance of 66 $cal.min^{-1}.°C^{-1}$. This suggests that the relatively slow response in fetal temperature during rapid temperature changes in the mother is a consequence of the heat capacity of the fetus and amniotic fluid, without any changes in the efficiency of heat transfer across the placenta. It also suggests the absence of a major increase in fetal metabolic rate (see below).

5.2 Respiratory blood gases

As noted above, several previous studies in sheep (8, 10, 14, 24) reported significant decreases in fetal arterial O_2 tensions during maternal exercise. Theoretical analysis suggests only minimal decreases in fetal O_2 tension when uterine blood flow is approximately 60% or more of its normal resting value (21), and observations during acute embolization of the uterine vascular bed indicate a similar relation. This is in good agreement with the finding of a significant but small (3 Torr) decrease in fetal O_2 tension during prolonged exercise at 70% $\dot{V}O_2$ max. Uterine blood flow did not decrease below 60% of its control value in any of the previous exercise studies (8, 10, 24) and therefore probably cannot fully explain the changes in O_2 tension observed in these studies.

In none of the previous studies were respiratory blood gas values corrected for the fetal body temperature at rest or for the changes during exercise. The failure to correct for a 1°C increase will result in about a 1.9 and 2.7 Torr underestimate for fetal O_2 and CO_2 tensions respectively, while pH will be 0.015 units too high (calculated from Severinghaus [34]). This partially explains the lower values for O_2 and CO_2 tensions and the higher pH values as reported in these studies. Nonetheless the blood gas changes during exercise as observed in these studies were larger than can be accounted for by the failure to make the required temperature corrections. After temperature correction the changes in these studies are of similar magnitude to those observed in the present study.

We found a larger decrease in fetal arterial O_2 content (27%) than in O_2 tension (11%) during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. In order to explain this observation we calculated the shift in the oxyhemoglobin dissociation curve (or P_{50}) during exercise and its effect on fetal O_2 content. Oxygen content and partial pressures are related by the modified Hill equation (16):
$\log {}^{P}O_2 = k_1 - k_2(pH-7.4) + k_3\log(s/[100-s])$, in which the constant k_1 represents the log ${}^{P}O_2$ at 50% saturation at pH 7.4. Values for P_{50} increase markedly with advancing gestational age, and reported values for fetal sheep vary from 16.0 Torr at 38°C (27) to 21.5 Torr at 37°C (5) or from 17.4 to 24.7 Torr at 39.5°C (see below) and pH 7.4. The effect of temperature on k_1 is given by $\Delta\log {}^{P}O_2 = 0.0244\,\Delta T$ for adult human blood (3), and we found a similar constant for fetal sheep blood in a preliminary study. We used this constant, k_2 and k_3 values of 0.363 and 0.305 (4), and the changes in temperature, pH, and O_2 tension and content as observed in the present study during 40 min exercise at 70% $\dot{V}O_2$ max to calculate a mean P_{50} in our fetuses. P_{50} was 22.8 Torr at rest (39.5°C) and 24.5 Torr during exercise (40.8°C) at pH 7.4; or 24.4 and 25.8 Torr at measured fetal pH values of 7.32 and 7.34, respectively. While the temperature effect alone would have resulted in a reduction in O_2 saturation from 55.8% to 49.9%, the combined temperature and pH effects should have reduced the O_2 saturation to only 51.3%. Therefore the shift in the oxyhemoglobin dissociation curve can account for only 30% of the decrease in O_2 content. The remaining 70% of the decrease in O_2 saturation, to 41.3%, results from the 3 Torr decrease in O_2 tension.

5.3 Uterine oxygen consumption

During periods of moderate uterine blood flow restriction, O_2 extraction can increase markedly and uterine O_2 consumption can be maintained (9). This is in good agreement with our observations during exercise and with similar findings by Clapp (10) and Chandler and Bell (8). When uterine blood flow decreases during exercise, preferential shunting occurs within the uterus, favoring cotyledonary flow at the cost of myometrial flow (13, 18). Therefore it is likely that during exercise the combined fetal and placental O_2 consumption is maintained at, or is slightly increased above, control levels.

According to the Van 't Hoff-Arrhenius' law total uterine O_2 consumption should increase during exercise. We observed an insignificant increase of 6% in uterine O_2 consumption during prolonged exercise. Assuming a Q_{10} of 2 to 3, the increase in fetal metabolism should have been 9 to 16% and the metabolism of placenta and uterine wall should have increased by 11 to 18%. However, pH change or substrate limitation may prevent expression of the increased enzymatic reaction rate as expected from the Q_{10} effect. Furthermore, it has been argued that the Van 't Hoff-Arrhenius' law may be masked by CNS regulation, as has been shown to occur in poikilothermic species (7). Therefore it is impossible to assess accurately to what extent the fetal and placental O_2 requirements should have increased during exercise. Fetal O_2 tension decreased by 3 Torr but remained within normal limits. On one hand this suggests that the fetal requirements during prolonged exercise are not met to the same extent as at rest. On the other hand, the absence of signs of fetal "stress" or hypoxia (see below) suggests that fetal oxygenation during maternal exercise remains within normal limits.

5.4 Glucose, lactate and pyruvate

Our results confirm recent studies by Clapp (10) and Chandler and Bell (8) showing increased maternal and fetal lactate concentrations during prolonged exercise in pregnant sheep. In addition, our study shows that during short-term exercise fetal values do not change significantly despite increased maternal levels. Since glucose and lactate are actively metabolized by both the fetus and the placenta, it is difficult to assess the physiologic importance of increased plasma concentrations. The study by Chandler and Bell (8) showed that uterine uptake of glucose and lactate does not change during exercise. If this is true, the increase in fetal lactate concentration during exercise must be due to increased delivery of lactate by the placenta, increased fetal production of lactate, or reduced consumption of lactate, or a combination of these factors. Umbilical uptake studies are necessary to indicate the physiologic importance of increased fetal lactate levels during exercise.

5.5 Placental diffusing capacity

Gilbert et al (15) reported that resting placental CO diffusing capacity is lower in chronically exercised guinea pigs than in nonpregnant controls. Further studies in guinea pigs showed that the CO diffusing capacity correlated linearly with both maternal and fetal placental exchange surface area (36) and the amount of daily exercise (28). However, we found no acute changes in placental diffusing capacity during exercise as compared to the pre-exercise control period.

5.6 Catecholamines

Jones (20) reported that hypoxia is one of the most potent stimuli for catecholamine release in fetal sheep and is accompanied by changes in heart rate and blood pressure. We found a twofold increase in fetal norepinephrine concentrations in response to maternal exercise. The changes were not significant because of the relatively large variability in control and exercise values. The epinephrine and dopamine concentrations remained below the sensitivity of the assay. The absence of a consistently large increase in fetal catecholamines is in good agreement with two previous preliminary reports (17) and indicates the absence of hypoxia or other "stress" in the fetus during maternal exercise.

5.7 Heart rate and arterial pressure

Fetal heart rate response to maternal exercise has been studied in humans since Hon and Wohlgemuth (19) proposed it as a clinical test for "uteroplacental insufficiency". Although several investigators (19, 29, 37) reported changes in fetal heart rate patterns in relation to maternal exercise, mean fetal heart rate changes were not significant, and the test is no longer in clinical use. In sheep, Emmanouilides et al (14) reported that fetal heart rate increased from 152 to 171 bpm during maternal exercise. However, observations by Clapp (10) and ourselves do not confirm such changes.

Our findings confirm previous observations (10, 14) that fetal arterial blood pressure does not change during maternal exercise. The absence of fetal heart rate and blood pressure changes also suggests the absence of catecholamine release in the fetus during maternal exercise.

5.8 Cardiac output and blood flow distribution

Fetal cardiac output is not markedly affected by norepinephrine infusion (25) or hypoxia (23), but its distribution is altered, favoring placenta, heart, and lungs (norepinephrine); or brain, heart, and adrenal glands (hypoxia). We observed no significant change in either cardiac output or blood flow distribution. This confirms the absence of any marked catecholamine release or hypoxia in the fetus during maternal exercise.

5.9 Blood volume

Packed cell volume increases in the fetus during hypoxia and enhances the oxygen carrying capacity and the hydrogen ion buffering capacity of the blood (35). Chandler and Bell (8) found no change in fetal hematocrit during maternal exercise. We also observed no change in fetal hematocrit, nor did we find a change in fetal total blood, plasma, or red cell volumes during exercise. This is additional circumstantial evidence for the absence of fetal hypoxia during maternal exercise.

6. Significance

During maternal exercise uterine O_2 consumption is maintained despite a marked reduction in uterine blood flow, as a result of hemoconcentration and increased uterine O_2 extraction. This probably indicates that fetal oxygen consumption is maintained at the pre-exercise level. We found a 3 Torr decrease in fetal arterial O_2 tension and a 1.5 $ml.dl^{-1}$ decrease in O_2 content during maternal exercise, with full recovery within 20 min. However, this did not result in major cardiovascular changes or catecholamine release in the fetus. Therefore our study suggests that maternal exercise does not represent a major stressful or hypoxic event to the fetus. Umbilical uptake studies of oxygen and nutrients are needed for a more complete understanding of the acute and chronic effects of maternal exercise on the fetus.

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CHAPTER FOUR

The interactions of exercise and pregnancy: A review

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1. Abstract

Increasing numbers of women engage in relatively strenuous exercise during pregnancy. The interaction of the increased metabolic demands of physical activity with those of pregnancy is poorly understood. We review what is known and what is not known of the extent to which pregnancy affects a woman's ability to perform strenuous activity, and the extent to which exercise affects the pregnant woman, the fetus, and the infant.

2. Introduction

When the stress of strenuous physical activity is superimposed upon that of pregnancy, the metabolic demands of the gravid uterus may come in conflict with those of the exercising muscles. This may result in reduced exercise performance of the mother and/or adverse effects, including acute fetal distress. It is also possible that the repeated stress of daily exercise results in fetal growth retardation.

Because little is known about this field we will review present knowledge of the physiology of exercise during pregnancy. The two main questions which we will consider concern first the extent to which pregnancy affects a woman's ability to perform strenuous activity, and then the extent to which exercise affects the pregnant woman, the fetus, and the infant. Ancillary questions include the following: 1) To what extent does total maternal oxygen consumption during physical activity differ from that in nonpregnant individuals? 2) Is one's physical working capacity affected by pregnancy? 3) To what extent are uterine blood flow and uterine oxygen consumption altered by exercise? 4) What is the significance of temperature changes for the mother and fetus? 5) To what degree does exercise

affect maternal and fetal respiratory blood gases? 6) Is there evidence for acute fetal distress during exercise? 7) Is fetal outcome affected by repeated strenuous physical activity during pregnancy? In this review we will briefly consider these questions. A more complete exposition is given elsewhere (44).

Before dealing with these questions, however, we would like to point out some of the problems associated with the study of the physiologic effects of exercise during pregnancy. First, pregnancy affects maternal body weight, dimensions, and composition and consequently the baseline values of many physiologic variables relevant to the study of exercise. Second, these changes also affect the physiologic burden of a given exercise regimen on the individual. This is obvious in weight-bearing exercise (e.g. treadmill, steptest). However, the amount of energy required to pedal a bicycle ergometer (nonweightbearing exercise) may also increase because of fluid accumulation in the legs and perhaps because of other factors. Third, the physiologic response to a fixed exercise regimen shows a wide variation between individuals. By standardizing the exercise level to a percentage of the indidivual's maximal oxygen consumption (% $\dot{V}O_2$ max) rather than to a fixed external task, this apparent variation can be minimized. Although this standardization is commonly used in physiologic studies, few authors have used it in pregnant subjects (42, 43, 74). Fourth, because many variables affect both pregnancy and exercise few, if any, studies on the combined subject can be considered well controlled. Fifth, only a limited number of studies have been reported under the most strenuous circumstances, i.e., exhaustive exercise near term. Therefore, it is not known to what extent exercise responses differ as a result of pregnancy per se. For similar reasons there are no data on fetal outcome under these circumstances. Sixth, most reliable physiologic data are derived from animal studies. However, the results of such studies may be of limited applicability to humans because quadrupeds (in which most such studies are performed) are less subject to venous pooling than are humans, tend to eliminate heat by a different mechanism – panting versus sweating – and can not necessarily be motivated to perform exhaustive exercise in the absence of other stress, as are humans. Seventh, the performance of such studies in humans presents ethical and legal problems. Therefore, while knowledge of the interactions of pregnancy and exercise must be derived from both clinical studies in human volunteers and laboratory studies in experimental animals, all such studies present problems and have limitations.

3. Maternal oxygen consumption

During pregnancy resting O_2 consumption increases with advancing gestational age to a maximum value near term 16 to 32% above nonpregnant values (55, 73). This higher value results largely from the increased uterine tissue mass, including that of the fetus. Maternal O_2 consumption is increased only 4% above that of the nonpregnant state after subtracting for the total uterine contents (11). Thus, the metabolic rate of the other maternal tissues is virtually unaffected by pregnancy despite a slight increase in cardiac and respiratory work.

Because O_2 consumption increases with both exercise level and gestational age, the most pronounced increases in O_2 consumption can be expected during maximal exercise near term. Submaximal exercise during late gestation is associated with approximately 10% higher absolute values for O_2 consumption than is exercise during the nonpregnant state, both during weightbearing exercise in humans (34), and goats (14), and during nonweightbearing exercise (4, 16, 19, 27, 34, 38, 55, 73).

The amount of oxygen required for exercise can be calculated by subtracting the resting O_2 consumption from the total O_2 consumption during and following exercise. During pregnancy higher values have been reported for treadmill exercise (14, 34, 72), as would be expected because of the pregnancy weight increase. In contrast, nonweightbearing exercise during pregnancy does not consistently increase the O_2 requirements (Table 1). This suggests that exercise efficiency is not greatly affected by pregnancy, either by body position and composition or by the metabolic and endocrinologic changes.

Because all "normal" weightbearing activities during pregnancy require a higher energy output, some training effect seems inevitable unless a more sedentary life style is adopted. In the nonpregnant individual physical training increases $\dot{V}O_2$ max up to 33%. To what extent $\dot{V}O_2$ max is affected by pregnancy has not been measured in either sedentary or trained pregnant women. The only controlled study during pregnancy was done in rats (75), showing 7% $\dot{V}O_2$ max increase in sedentary pregnant rats, and a 13% increase in the trained animals, both changes not being statistically significant. Rats which were trained both prior to and during pregnancy had 23% higher $\dot{V}O_2$ max values than sedentary rodents, but the increase during pregnancy accounted for only 8% of the total. During pregnancy O_2 consumption can increase 5- to 6-fold with maximal exercise in ewes (42), but it is unknown whether or not this increase is greater than that in nonpregnant sheep.

4. Physical working capacity

If one could extrapolate from the above observations at submaximal work levels in humans, a given maximal task during pregnancy would require about a 10% higher absolute value for $\dot{V}O_2$ max, which seems possible for otherwise sedentary individuals. This suggests that objectively such women should be able to maintain the same tasks as they did prior to pregnancy. However, working capacity is affected not only by $\dot{V}O_2$ max, but also by a variety of conditions, including somatic factors, environmental factors, work characteristics, training and adaptation, and psychic factors, including motivation. This makes it difficult, if not impossible, to draw definitive conclusions as to the physical working capacity during pregnancy. Although maximal O_2 consumption is a most important variable in exercise physiology, it has not been studied in pregnant humans. Because of the hemodynamic changes during pregnancy, including increased blood volume, it is conceivable that $\dot{V}O_2$ max may not only increase in sedentary individuals, but that training may increase $\dot{V}O_2$ max beyond its nonpregnant limits. Further study of this important variable is clearly indicated, particularly in humans.

Table 1. Oxygen consumption during bicycle exercise in the sitting position.

Author, year	Subjects	Oxygen Consumption					
		Rest		Exercise		Exercise—Rest	
		Absolute ($ml.min^{-1}$)	P-NP (%)	Absolute ($ml.min^{-1}$)	P-NP (%)	Absolute ($ml.min^{-1}$)	P-NP (%)
Ueland et al, 1973	P	330	17	836	15	506	13
	NP	281		728		447	
Knuttgen and Emerson, 1974	P	249	30	1060	3	811	−3
	NP	191		1030		839	
Pernoll et al, 1975	P	331	33	1167	15	836	8
	NP	248		1019		771	
Lehmann and Regnat, 1976	P	340	16	1265	11	925	9
	NP	293		1141		848	
Edwards et al, 1981	P	243	27	883	4	640	−2
	NP	191		847		656	

P, Pregnant; NP, Nonpregnant.

5. *Uterine oxygen consumption*

Uterine blood flow increases with advancing gestational age, although flow decreases somewhat per kilogram of total uterine contents. The flow increase results from a decrease in uterine vascular resistance secondary to vasodilatation associated with increasing concentrations of estrogens produced by the fetoplacental unit and prostaglandins (PGE_2 and PGI_2) produced by the vessel wall (74).

Although the dilated uterine vasculature during pregnancy is less sensitive to the effects of vasoconstrictive agents than in the nonpregnant state, it responds to circulating prostaglandins and catecholamines and to sympathetic stimulation. Uterine blood flow may decrease spontaneously up to 20% (37), and reductions up to 50% have been reported in response to alkalosis and hyperthermia (51) and to a variety of other stresses (66). It has been suggested that these vasoconstrictive occurrences are catecholamine mediated, but this has not yet been demonstrated.

During exercise the redistribution of cardiac output has been thought to result from vasodilatation in exercising muscles, mediated by local metabolic factors, and from sympathetic vasoconstriction in tissues with a high resting flow and low O_2 extraction, such as the splanchnic bed and non-working muscles (61).

Because the uterine vasculature during pregnancy is sensitive to sympathetic stimulation and catecholamine release, one would also expect a reduction in uterine blood flow during maternal exercise. Using the disappearance of ^{24}Na injected into the myometrium, Morris et al (47) suggested a 25% reduction in flow to the human pregnant uterus during mild short-term bicycle exercise in the supine position. However, this probably represents an overestimate because the myometrium is more sensitive to catecholamines than is the placenta (26), resulting in flow redistribution within the uterus, favoring cotelydonary flow at the expense of myometrial flow (13, 30).

Lotgering et al (42) studied uterine blood flow at different levels (% $\dot{V}O_2$ max) and durations of exercise in sheep. As shown in Figure 1a, uterine blood flow decreased immediately at the onset of exercise, was significantly below control values throughout the exercise period, and returned to control levels within 10 min of recovery. Flow decreased 13% during a 10-min exercise period at 70% $\dot{V}O_2$ max, 17% during a 10-min exercise period at 100% $\dot{V}O_2$ max, and 24% near the end of a 40-min exercise period at 70% $\dot{V}O_2$ max. Regression analysis showed a significant decrease in flow with exercise time, and flow varied linearly with heart rate, where heart rate is linearly related to the level of exercise. Thus, it is likely that uterine blood flow decreases with both the level and the duration of exercise. Hohimer et al (30), Clapp (10), and Chandler and Bell (9) also have reported decreases in uterine blood flow of up to 36% during exercise. Other investigators (13, 52) have concluded that uterine blood flow in sheep remains constant during treadmill exercise. However, their measurements were made shortly after, rather than during, exercise, and uterine flow returns rapidly to control levels when exercise is discontinued (42).

Although a reduction in uterine blood flow suggests a reduction in the supply of

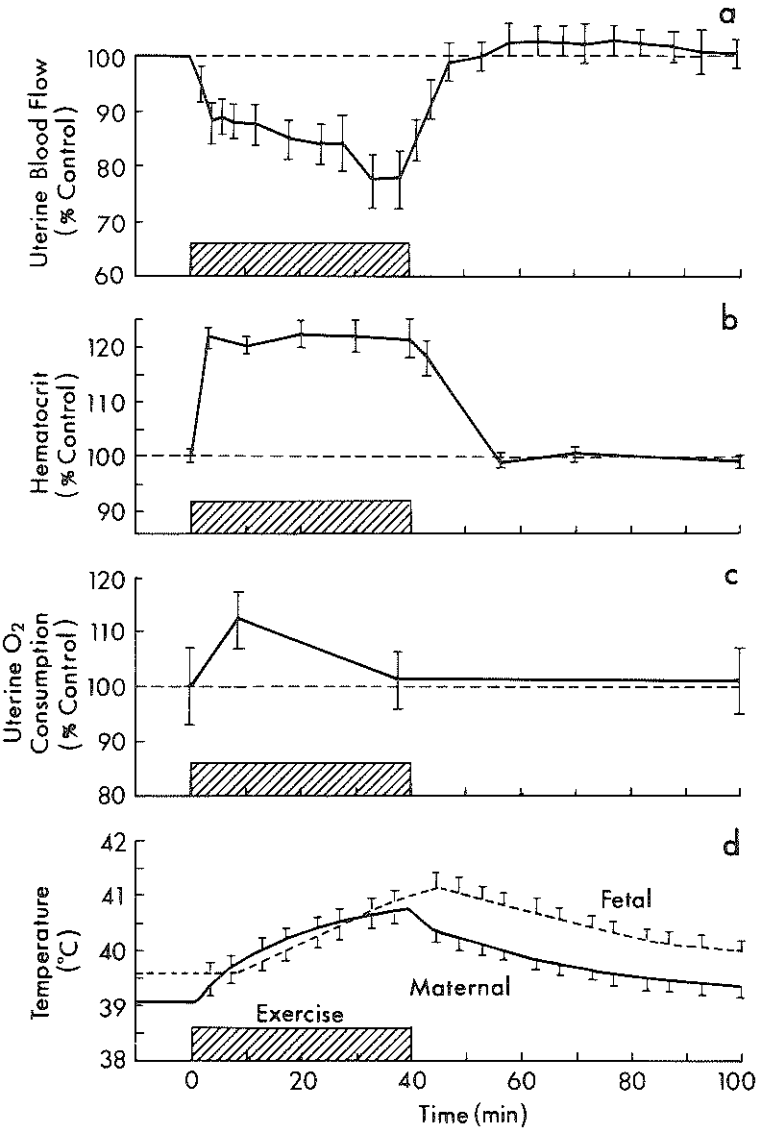

Figure 1. Physiologic changes for several functions in response to 40-min exercise at 70% $\dot{V}O_2$ max in pregnant sheep. A. Uterine blood flow (% control), B. Hematocrit (% control), C. Uterine oxygen consumption (% control), D. Maternal and fetal temperatures. Values are means ± SEM (n=8 [a,b,c] or 6 [d]).

oxygen and nutrients to the uterus and/or a reduction in oxygen consumption, this result is not necessarily true during exercise, because exercise is associated with a marked rise in maternal hematocrit. During exercise plasma filtrate is forced across the capillary membrane in exercising muscles, resulting in a decrease of up to 14% in plasma volume in man (25) and up to 20% in pregnant sheep (42), while the red cell mass remains constant (42). This hemoconcentration is associated with an increase in hemoglobin concentration (shown as hematocrit in Figure 1b), and thus of blood O_2 carrying capacity. Consequently, the reduction in oxygen delivery (O_2 content $\times$ flow) to the uterus is much smaller than the decrease in blood flow would suggest (42). In addition, the blood flow is redistributed within the uterus, favoring the placental cotelydons at the expense of the myometrium (13, 30), and oxygen extraction is increased (43). The net result of these compensatory mechanisms is a constant O_2 uptake by the uterus as a whole (Fig. 1c) (9, 10, 43) and by the fetus (10).

6. Temperature changes

During exercise the total heat production may increase as much as 20 times resting values. Only 20 to 25% of the added energy expenditure is used for external work, while the remaining 75 to 80% is transformed into heat. Although most of the heat is lost to the environment, some is stored, resulting in increased body temperature. Under normal resting conditions the temperature of the fetus is about 0.5°C higher than that of the mother in humans (2), baboons (46), and sheep (1, 43). Most of the fetal heat is transferred to the mother across the placenta and a smaller proportion across the fetal skin, amniotic fluid, and uterine wall (1, 2). Recent theoretical studies (63) suggest that the maternal body temperature is the major determinant of fetal temperature, while changes in uterine blood flow or fetal metabolism are quantitatively less important.

In studies of exercising sheep from our laboratory (43) the fetal temperature lagged behind the rapidly changing maternal temperature at the onset and cessation of exercise (Fig. 1d). Consequently the fetal-maternal temperature difference during the onset of exercise was reduced or even reversed, while a larger temperature difference existed following exercise. These changes were more pronounced with higher levels of exercise when the maternal temperature increases more rapidly. Return of the fetal temperature to control values was slow, requiring over one hour following prolonged (40 min) exhaustive exercise at 70% $\dot{V}O_2$ max (Fig. 1d).

Among the possible physiologic implications of increased body temperature are increased metabolism (Q_{10} effect), rightward shifts of the maternal and fetal oxyhemoglobin dissociation curves, and a reduction of uterine blood flow. However, the quantitative aspects of these changes are not yet fully understood and require further study (44). Knowledge of the maternal and fetal temperatures is essential for the correct interpretation of fetal blood gas measurements. Blood obtained anaerobically and analyzed for respiratory blood gases at a temperature

below that of the body shows a rise in pH and a fall in O_2 and CO_2 tensions (64). The failure to correct for a 1°C increase has been estimated to result in about a 1.9 and 2.7 Torr underestimate for fetal O_2 and CO_2 tensions, respectively, and a pH that is falsely 0.015 units too high (43). All factors which change maternal temperature, uterine or umbilical blood flows, or fetal metabolism may affect the temperature gradient, especially in the nonsteady state. Unfortunately, this often is not taken into account in studies of fetal blood gas values.

7. Respiratory blood gases

When the proper temperature corrections are made, maternal O_2 tension and O_2 content increase and CO_2 tension decreases as a result of exercise induced hyperventilation and hemoconcentration. As shown in Figure 2, maternal O_2 tension increases 13% and O_2 content increases 25%, while CO_2 tension decreases 28% in sheep exercised to exhaustion at 70% $\dot{V}O_2$ max (43). Consequently the O_2 carrying capacity of the maternal blood is increased and the O_2 transport across the placenta is enhanced.

The reduced uterine blood flow during exercise, however, will tend to lower the placental O_2 transport. Theoretical analysis suggests only minimal decreases in fetal O_2 tension when uterine blood flow is approximately 60% or more of its normal resting value (41), and observations in our laboratory during acute

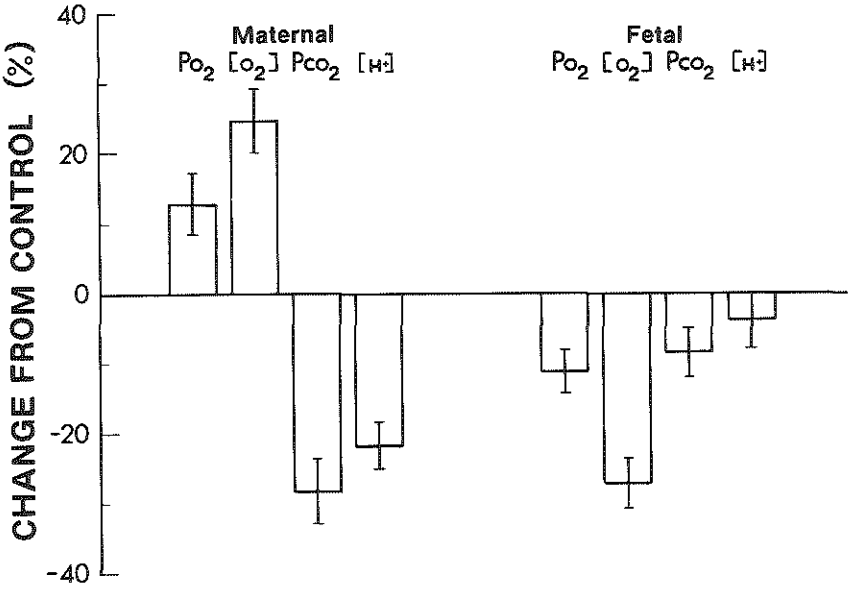

Figure 2. Percent changes in maternal and fetal respiratory blood gas concentrations during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max in sheep (after Lotgering et al [43]). Values are means ± SEM (n=12).

embolization of the uterine vascular bed suggest a similar relation. Nonetheless, several studies in exercising sheep (9, 10, 20, 40) have reported reductions in fetal arterial O_2 and CO_2 tensions of as much as 25%. Failure to correct the blood gas values for the temperature changes largely explains the difference in results between these studies and the smaller changes as observed by Lotgering et al (43). In the latter study (43) fetal arterial O_2 and CO_2 tensions and O_2 content decreased with the level and the duration of exercise, but the values differed significantly from control only when the ewes were run to exhaustion. During prolonged (40 min) exhaustive exercise at 70% $\dot{V}O_2$ max fetal aortic O_2 tension decreased 3.0 Torr (to 23.2 from 26.2 Torr), CO_2 tension 4.5 Torr (to 49.6 from 54.1 Torr) and O_2 content 1.5 $ml.dl^{-1}$ (to 4.3 from 5.8 $ml.dl^{-1}$), while pH increased 0.02 units. The percent changes are shown in Figure 2. Theoretical calculations suggest that about 30% of the decrease in O_2 saturation can be accounted for by the temperature and Bohr shifts of the oxyhemoglobin dissociation curve, whereas the remaining 70% of the decrease in O_2 saturation is associated with the 3 Torr decrease in O_2 tension (43). Although fetal O_2 tension and content decrease with exercise, this does not necessarily indicate that the fetal metabolic demands are not met or that the fetus is in "distress".

8. Other fetal responses

Fetal hypoxia and/or "distress" may be associated with changes in any of the following fetal variables: heart rate (6), blood pressure (6), cardiac output and its distribution (3), hematocrit (65), and catecholamine concentration (32).

Several authors (17, 18, 31, 36, 45, 54, 57, 58, 68, 69) have studied the fetal heart rate prior to, and following, a mild to moderate exercise stress of short duration. They noted only small changes in mean fetal heart rate and heart rate patterns, changes which were inconclusive as to possible "distress". However, it is conceivable that the fetal responses to maternal exercise recover rapidly following such a minimal stress. One study (67) reported a slightly higher fetal heart rate during short-term treadmill exercise as compared to baseline and recovery values, but the mean values were not compared statistically. This is also true for a study (28) in which higher fetal heart rates were found during the recovery from prolonged, moderately strenuous, exercise (1.5 miles jogging) in seven women. In neither study did the fetal heart rate pattern show any signs of "distress". One study reported on the changes in fetal heart rate both during and following 25-min bicycle exercise at about 70% $\dot{V}O_2$ max (12). The auscultated heart rate demonstrated only a mean 3 to 4 bpm increase during and following exercise, which is physiologically insignificant. In sheep, one investigator (20) observed an increased fetal heart rate, but others have reported no significant changes during either short-term (43) or prolonged exhaustive exercise (10, 43, 53).

The other fetal cardiovascular variables are also largely unaffected by maternal exercise. Fetal arterial blood pressure is unaffected by short-term (43) as well as

prolonged exercise in sheep (10, 20, 43, 53). Cardiac output and cardiac output distribution are unaffected by exhaustive shortterm exercise (43), but cardiac output has not been studied during prolonged exercise in sheep. One study (10) reported a 10% reduction in umbilical blood flow during prolonged exhaustive exercise. However, this observation needs to be confirmed because the reported resting value of 354 $ml.min^{-1}.kg^{-1}$ was well above accepted normal values. In addition, fetal hematocrit (9, 43) and red cell and plasma volumes (43) are unaffected by prolonged exercise.

The number of studies of fetal cardiovascular responses to maternal exercise is limited, but the available evidence suggests the absence of hypoxia or "stress". In addition, fetal catecholamine concentrations are not significantly increased in fetal sheep during both short-term(43) and prolonged exercise (29, 43, 53). However, extrapolating these responses from fetal sheep to the human fetus may not be legitimate for the reasons detailed above.

9. Fetal outcome

The effect on fetal outcome of a single factor such as exercise is easily obscured by the wide normal variation in outcome caused by a multitude of variables, including genetic and socio-economic factors, nutrition, environmental factors, "stress", et cetera. Thus, the question of whether physical activity affects fetal outcome can only be answered by large, well controlled prospective epidemiologic studies. We know of no such study in pregnant women.

However, several studies concerning this subject are nonetheless worthy of discussion. A high level of voluntary daily exercise or a high "physical fitness score" was found not to be associated with low Apgar scores or low birth weights in humans (22, 59). Adverse effects on fetal outcome were not observed in a small prospective study in which the mothers exercised at about 70% $\dot{V}O_2$ max three times weekly during the second and third trimester (12). The effects of strenuous exercise during human pregnancy have been studied mainly in athletes (8, 15, 21, 23, 28, 35, 50, 56, 62, 76) and all these studies report normal or improved fetal outcome. Although these studies were retrospective and/or uncontrolled, with the women in excellent condition prior to pregnancy, they suggest the absence of major negative effects of strenuous exercise on fetal outcome in healthy women. Strenuous exercise is normal during late gestation in many large game mammals and their predators as well as in some domestic animals (7). This suggests that strenuous voluntary activity during pregnancy does not adversely affect fetal outcome in healthy individuals of many species.

In contrast, adverse effects of maternal physical activity on fetal outcome have been reported both in humans and laboratory animals. The most commonly mentioned negative effect is low birth weight. Several studies have reported a decrease of as much as 400 grams, and an increased incidence of low birth weight infants in offspring of working mothers (24, 48, 60, 70). However, this may reflect

the poor nutritional status of these women (48), or other selection factors, rather than represent the effect of physical activity per se. Weight reduction has also been reported in pregnant laboratory animals which were forced to exercise strenuously during pregnancy. An 8% reduction was reported in forcefully exercised mice (71) and guinea pigs (49). Fetal weight in rats forced to swim was 6% lower than normal (39); however, rats forced to run did not show growth retardation (5). A 12 to 20% reduction in fetal weight was also reported in exercised pygmy goats (14), but this study may not have been well controlled. Because fetal growth retardation has been associated not only with increased maternal physical activity but also with restriction of activity (33), one cannot exclude the possibility that the "stress" of fear and handling related to forced exercise in a laboratory environment, rather than the exercise per se, contributed to the growth retardation. A variety of other adverse effects has also been suggested, including increased perinatal mortality and increased incidence of prematurity (24). However, further well matched prospective studies are necessary to confirm any such effects. This is also true for the possible teratogenic effect of increased temperature during exercise in early pregnancy.

It is apparent that exercise might have positive or negative health effects during pregnancy. Figure 3 presents a scheme of the manner in which this might occur. The ordinate indicates such health effects without numerical values. The product of

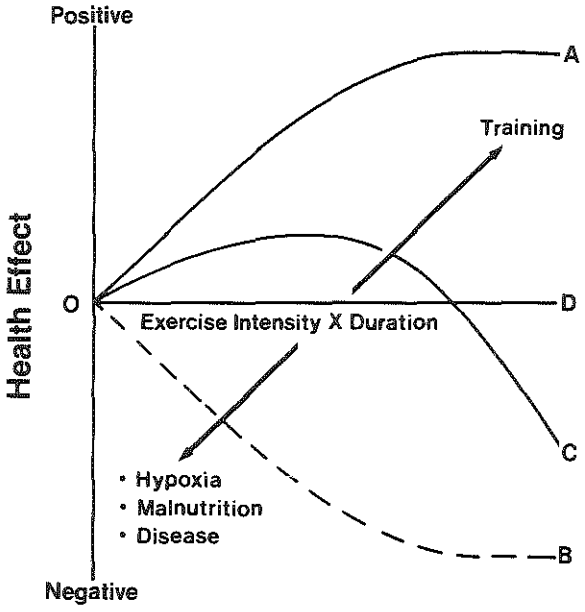

Figure 3. Diagramatic representation of how exercise intensity and duration might have positive or negative effects on certain physiologic functions or outcomes during pregnancy. (See text for details).

exercise intensity and duration as a rough approximation of overall work or effort is shown on the abcissa. Line A indicates those effects which are beneficial and tend to increase as a function of exercise intensity and duration. Line B indicates the opposite effects. Line C indicates that for some functions there may be a positive effect at low to moderate exercise levels, but that this decreases or reverses at higher levels. Finally, Line D suggests that for some functions there is no discernable effect. In addition, the figure suggests that training may shift the curves upward and to the right. For instance, in a woman who is thoroughly conditioned a given exercise level may result in greater health benefits, or the same benefits at a higher level of intensity and/or duration. In contrast, other stresses such as hypoxia, malnutrition, or certain disease states, may compete for the subject's physiologic reserves, shifting the curve downward and to the left. In that instance adverse effects would be more common at low exercise levels.

10. Summary and conclusions

Physical activity during pregnancy results in marked cardiovascular adjustments in the mother, including a reduction in uterine blood flow. However, because of simultaneous hemoconcentration and increased O_2 extraction, uterine O_2 consumption remains constant. In contrast to relatively profound physiologic changes in the mother, the changes in the fetus are small. The O_2 tension and O_2 content in fetal arterial blood decrease slightly. However, other fetal variables, including catecholamine concentrations, heart rate, blood pressure, cardiac output, blood flow distribution, and blood volume, remain virtually constant. This suggests that acute exercise does not represent a major hypoxic or other stress to the fetus. Little is known about the physiologic effects of chronic exercise on the fetus. The most likely possible effect is a small reduction in birth weight, at least in some species. Large, well controlled prospective epidemiologic studies are necessary to establish possible positive or negative effects in humans. Finally, further physiologic studies are needed for a more complete understanding of the remarkably effective homeostatic mechanisms in both mother and fetus during maternal exercise.

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Summary

This thesis consists of four papers dealing with various aspects of maternal and fetal physiology of exercise during pregnancy.

CHAPTER ONE comprises an extensive review of the literature on this subject as well as recommendations for further investigations. During pregnancy resting oxygen consumption increases with the increase in body weight, but the increase in oxygen consumption with exercise is greater in pregnant than in nonpregnant women only if the body weight is carried. These facts should be taken into account if one wants to normalize oxygen consumption for body size. The maximal oxygen consumption in pregnant women has not been measured. From the fact that during pregnancy maternal heart rate and cardiac output are increased at rest as well as at submaximal exercise, it is often concluded that maximal oxygen consumption and maximal working capacity are reduced. However, this is only true if maximal heart rate and maximal cardiac output are constant and the relation between these variables and oxygen consumption does not change as a result of pregnancy, which as yet has not been proven.

Probably as a result of catecholamine release, uterine blood flow decreases during physical exercise, despite a slight increase in mean arterial pressure. However, the flow of oxygen to the placenta does not decrease to the same extent, because of blood flow redistribution within the uterus, and hemoconcentration. Because of these compensatory mechanisms and the simultaneous increase in oxygen extraction, uterine oxygen consumption does not change significantly during exercise.

The membrane characteristics of the placenta, measured as the carbon monoxide diffusing capacity, are not acutely influenced by physical exercise. Therefore, transfer of gases across the placenta during exercise is determined by the partial gas pressures and by the blood flow in the maternal and fetal exchange vessels. Because of the relative hyperventilation which occurs during exercise in pregnancy, the maternal O_2 tension increases and CO_2 tension decreases. The pH rises initially, to subsequently decrease progressively as a result of lactate accumulation. Fetal O_2 and CO_2 tensions fall slightly and the pH increases somewhat, while fetal O_2 content shows a moderate decrease. These changes in the fetus can only in part be explained by the effects of changes in pH and temperature on the dissociation curve of oxyhemoglobin. They suggest alterations in oxygen requirement or in the supply of oxygen to the fetus, despite the absence of changes in total uterine oxygen consumption. Uterine glucose uptake and lactate production do not appear to be significantly influenced by maternal exercise. Lactate is an important substrate of aerobic metabolism in the fetus. The high lactate concentration without fall in pH, as observed during exercise, probably reflects the high maternal concentration

without implying increased anaerobic metabolism in the fetus. The absence of significant acute changes in fetal catecholamine concentrations and in the cardiovascular system of the fetus suggests that maternal exercise does not represent a major "stress" to the fetus.

It is likely that physical training before and/or during pregnancy will result in an increased maximal oxygen consumption, as it does in nonpregnant women. However, it is unknown if there is a shift of the absolute upper limit as a result of pregnancy. With a good physical condition each task represents a smaller acute physiologic load than with a poor physical condition, which seems beneficial to the fetus. On the other hand, physical condition improves only with repeated exercise of adequate intensity. Therefore, it is conceivable that physical training in pregnancy is associated with adjustments that affect the fetus. Various effects on the fetus, beneficial as well as detrimental, have been attributed to repeated strenuous maternal exercise, but they are still disputed. Large prospective studies including appropriate controls are required to conclusively answer the question, if any such effects indeed do exist.

CHAPTER TWO deals with an experimental study in chronically instrumented sheep of the acute effects of exercise on maternal oxygen consumption, cardiac output, uterine blood flow, and blood volume. A modification is described of the usual method of measuring uterine blood flow with electromagnetic flowprobes. The flowprobe is placed around the common internal iliac artery, which allows measurement of virtually all blood flowing to the pregnant uterus. To minimize variations resulting from differences in physical condition, the exercise level was expressed as a percentage of maximal oxygen consumption (% $\dot{V}O_2$ max) instead of as the amount of external work.

During maximal exercise the maternal oxygen consumption increased almost sixfold, cardiac output threefold, and arteriovenous oxygen content difference twofold. The mean blood flow to the uterus fell and the vascular resistance increased with an increasing level and duration of exercise. Maximal changes in blood flow and resistance of 24 and 65%, respectively, were observed at exhaustion during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. Maternal blood volume decreased on the average 14% and the hematocrit increased 21% immediately at the onset of exercise. No change occurred during the further 40 min of exercise at 70% $\dot{V}O_2$ max. The observed hemoconcentration is important for maintaining oxygen supply to the uterus during physical exercise.

CHAPTER THREE describes an experimental study in chronically instrumented sheep of the acute effects of exercise on uterine oxygen consumption, on the maternal and fetal respiratory blood gas tensions and carbohydrate concentration, on the placental diffusing capacity, and on the fetal catecholamine concentration and the cardiovascular system. Because of the occurrence of hemoconcentration and increased oxygen extraction, total oxygen consumption of the pregnant uterus does not decrease during exercise, despite a marked reduction in uterine blood flow. The

changes in maternal and fetal body temperatures and respiratory blood gas values were most pronounced during prolonged (40 min) exercise at 70% $\dot{V}O_2$ max. Maternal and fetal temperatures showed a mean maximal rise of 1.5 and 1.3°C, respectively. After correction for the temperature changes, maternal O_2 tension increased 13.1 Torr and O_2 content 2.7 $ml.dl^{-1}$ during exercise, while CO_2 tension decreased 10.7 Torr. Fetal arterial O_2 tension decreased 3.0 Torr, O_2 content 1.5 $ml.dl^{-1}$, and CO_2 tension 4.5 Torr, whereas pH increased 0.02 units. The blood gas values returned to virtually baseline levels within 20 min. Maternal glucose, lactate, and pyruvate concentrations increased significantly, but in the fetus only the lactate concentration increased significantly. The diffusing capacity of the placenta for carbon monoxide, fetal catecholamine concentrations, heart rate, cardiac output, and blood flow distribution, and blood and plasma volumes did not change significantly. These observations suggest that maternal exercise does not represent a major "stress" to the sheep fetus.

CHAPTER FOUR comprises a brief review of the literature, with a summary of the results obtained in the experimental studies described in Chapters 2 and 3. The article aims at clinicians, focussing on the acute changes in maternal and uterine oxygen consumption, maternal and fetal temperatures and respiratory blood gas values, the fetal cardiovascular system, and the effects of chronic exercise on the condition of the newborn.

Further investigation is required to obtain a more complete picture of the remarkably effective homeostatic mechanisms which are operative in mother and fetus. Expansion of our understanding of the biologic processes during normal pregnancy may eventually lead to rational therapy in cases in which the homeostatic mechanisms fall short.

Samenvatting

Dit proefschrift bestaat uit een aantal artikelen, die verschillende aspecten behandelen van de moederlijke en foetale fysiologie van inspanning tijdens de zwangerschap.

HOOFDSTUK EEN omvat een uitgebreid literatuuroverzicht betreffende dit onderwerp, alsmede aanbevelingen voor verder onderzoek. Tijdens de zwangerschap neemt het zuurstofgebruik in rust toe met de toename in het lichaamsgewicht, maar de toename van het zuurstofgebruik bij inspanning is bij zwangeren alleen groter dan bij niet-zwangeren als het lichaamsgewicht wordt gedragen. Men dient met deze feiten rekening te houden als men het zuurstofgebruik wil standaardiseren voor lichaamsgrootte. Het maximale zuurstofgebruik bij zwangere vrouwen is nooit gemeten. Uit het feit, dat tijdens de zwangerschap de moederlijke hartfrequentie en het hartminutenvolume, zowel in rust als bij inspanning, zijn verhoogd, wordt vaak geconcludeerd dat het maximale zuurstofgebruik en het maximale werkvermogen verminderd zijn. Dit is echter alleen waar als de maximale hartfrequentie en het maximale hartminutenvolume constant blijven en het verband tussen deze variabelen en het zuurstofgebruik niet verandert als gevolg van de zwangerschap, hetgeen tot nu toe niet is bewezen.

Waarschijnlijk als gevolg van het vrijkomen van catecholamines vermindert de bloedstroom naar de uterus tijdens fysieke inspanning, ondanks een lichte stijging van de gemiddelde arteriële bloeddruk. De zuurstofstroom naar de placenta neemt daarbij echter niet in dezelfde mate af, als gevolg van redistributie van de bloedstroom binnen de uterus en hemoconcentratie. Vanwege deze compensatiemechanismen en de gelijktijdige toename van de zuurstofextractie, verandert het zuurstofgebruik van de uterus tijdens inspanning niet significant.

De membraaneigenschappen van de placenta, gemeten als de diffusiecapaciteit voor koolmonoxide, worden niet direct door fysieke inspanning beïnvloed. Daarom wordt de gasuitwisseling over de placenta bij fysieke inspanning bepaald door de partiële gasdrukken en door de doorstroming van de moederlijke en foetale vaten waar gasuitwisseling plaatsvindt. Als gevolg van de relatieve hyperventilatie, die optreedt tijdens inspanning in de zwangerschap, stijgt de moederlijke O_2 spanning en daalt de CO_2 spanning. Aanvankelijk stijgt daarbij de pH, om vervolgens progressief af te nemen ten gevolge van lactaatophoping. De foetale O_2 en CO_2 spanning dalen licht en de pH neemt iets toe, terwijl het O_2 gehalte van het foetale bloed een matige daling vertoont. Deze veranderingen bij de foetus kunnen slechts gedeeltelijk worden verklaard door de veranderingen in pH en temperatuur op de dissociatiecurve van oxyhemoglobine. Zij suggereren veranderingen in de zuurstofbehoefte of in de aanvoer van zuurstof naar de foetus, ondanks de afwezigheid van veranderingen in het totale zuurstofgebruik van de uterus. De

glucoseopname en lactaatproductie van de uterus lijken niet significant te worden gewijzigd door moederlijke inspanning. Lactaat is een belangrijk substraat voor de aerobe stofwisseling van de foetus. De hoge lactaatconcentratie zonder pH daling, zoals die bij de foetus wordt waargenomen tijdens inspanning, weerspiegelt daarom waarschijnlijk de hoge concentratie bij de moeder zonder te duiden op een toename van de anaerobe stofwisseling. De afwezigheid van significante acute veranderingen in de foetale catecholamine concentraties en in het cardiovasculaire systeem van de foetus suggereert, dat moederlijke inspanning geen grote "stress" voor de foetus betekent.

Waarschijnlijk zal fysieke training voor en/of tijdens de zwangerschap het maximale zuurstofgebruik doen toenemen, evenals dat bij niet-zwangere vrouwen het geval is. Het is echter onbekend of er een verschuiving plaatsvindt van de absolute bovengrens als gevolg van de zwangerschap. Bij een goede fysieke conditie betekent elke taak een geringere acute fysiologische belasting dan bij een slechte fysieke conditie, hetgeen gunstig lijkt te zijn voor de foetus. Aan de andere kant verbetert de fysieke conditie pas bij herhaalde inspanning van voldoende intensiteit. Het is daarom denkbaar, dat training in de zwangerschap gepaard gaat met aanpassingen, die de foetus kunnen beïnvloeden. Aan herhaalde zware lichamelijke inspanning van de moeder worden verschillende, gunstige zowel als ongunstige, effecten op de foetus toegeschreven, maar deze zijn nog onderhevig aan discussie. Grote prospectieve onderzoeken met passende controles zijn nodig om afdoende de vraag te beantwoorden, of dergelijke effecten inderdaad bestaan.

HOOFDSTUK TWEE behandelt een experimenteel onderzoek bij chronisch geïnstrumenteerde schapen naar de acute effecten van inspanning op het moederlijke zuurstofgebruik, op het hartminutenvolume, op de bloedtoevoer naar de uterus en op het bloedvolume. Een modificatie wordt beschreven van de gebruikelijke methode om de bloedtoevoer naar de uterus te meten met behulp van een electromagnetische flowmeter. De transducer van de flowmeter wordt rond de arteria iliaca interna communis geplaatst, hetgeen het mogelijk maakt om vrijwel de gehele bloedtoevoer naar de zwangere uterus te meten. Om de variatie tengevolge van verschillen in fysieke conditie zo klein mogelijk te maken, werd het inspanningsniveau uitgedrukt als percentage van het maximale zuurstofgebruik (% $\dot{V}O_2$ max), in plaats van als de hoeveelheid uitwendige arbeid.

Tijdens maximale inspanning steeg het moederlijke zuurstofgebruik bijna zesvoudig, het hartminutenvolume drievoudig en het arterioveneuze verschil in zuurstofgehalte tweevoudig. De gemiddelde bloedtoevoer naar de uterus nam af en de vaatweerstand nam toe met de toename van het niveau en de duur van de inspanning. Maximale veranderingen in de bloedtoevoer en de weerstand, van respectievelijk 24 en 65%, werden waargenomen bij uitputting tijdens langdurige (40 min) inspanning bij 70% $\dot{V}O_2$ max. Het moederlijke bloedvolume nam gemiddeld met 14% af en de hematocriet nam met 21% toe direct bij het begin van de inspanning. Er trad geen verandering op gedurende de verdere 40 min inspanning bij 70% $\dot{V}O_2$ max. De waargenomen hemoconcentratie is belangrijk

voor het handhaven van de zuurstoftoevoer naar de uterus tijdens fysieke inspanning.

HOOFDSTUK DRIE beschrijft een experimenteel onderzoek bij chronisch geïnstrumenteerde schapen naar de acute effecten van inspanning op het zuurstofgebruik van de uterus, op de moederlijke en foetale respiratoire bloedgaswaarden en koolhydraatconcentraties, op de diffusiecapaciteit van de placenta, en op de catecholamine concentraties en het cardiovasculaire systeem van de foetus. Wegens het optreden van hemoconcentratie en het toenemen van de zuurstofextractie verminderde het totale zuurstofgebruik van de zwangere uterus niet tijdens inspanning, ondanks een duidelijke afname van de doorstroming. De veranderingen in de moederlijke en foetale lichaamstemperatuur en de respiratoire bloedgaswaarden waren het meest uitgesproken tijdens langdurige (40 min) inspanning bij 70% $\dot{V}O_2$ max. De moederlijke en foetale temperatuur vertoonden een gemiddelde maximale stijging van respectievelijk 1.5 en 1.3°C. Na correctie voor de temperatuursveranderingen steeg de moederlijke arteriële O_2 spanning tijdens inspanning 13.1 Torr en het O_2 gehalte 2.7 $ml.dl^{-1}$, terwijl de CO_2 spanning 10.7 Torr daalde. De foetale arteriële O_2 spanning daalde 3.0 Torr, het O_2 gehalte 1.5 $ml.dl^{-1}$ en de CO_2 spanning 4.5 Torr, terwijl de pH 0.02 eenheden steeg. De bloedgaswaarden keerden binnen 20 min vrijwel geheel tot de uitgangswaarden terug. De moederlijke glucose-, lactaat-, en pyruvaatconcentraties namen significant toe, maar in de foetus nam alleen de lactaatconcentratie significant toe. De diffusiecapaciteit van de placenta voor koolmonoxide, de foetale catecholamine concentraties, de hartfrequentie, het hartminutenvolume, de verdeling van het hartminutenvolume en het bloed- en plasmavolume veranderden niet significant. Deze bevindingen suggereren dat moederlijke inspanning geen grote "stress" betekent voor de schapefoetus.

HOOFDSTUK VIER bevat een kort overzicht van de literatuur, met een samenvatting van de resultaten van de in hoofdstuk 2 en 3 beschreven experimenten. Het artikel richt zich op de clinici en beschrijft de acute veranderingen in het zuurstofgebruik van de zwangere en haar uterus, de moederlijke en foetale temperatuur en respiratoire bloedgaswaarden en het foetale cardiovasculaire systeem. Tevens beschrijft het de effecten van chronische inspanning op de conditie van de pasgeborene.

Verder onderzoek is nodig om een vollediger beeld te krijgen van de opvallend effectieve homeostatische mechanismen in moeder en foetus. Verdieping van ons begrip van de biologische processen tijdens de normale zwangerschap zal uiteindelijk kunnen leiden tot een rationele behandeling in gevallen, waarin de homeostatische mechanismen tekort schieten.

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