# Glucose and Lactate Kinetics During a Short Exercise Bout in Pregnancy

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**Pregnancy is considered diabetogenic. Although exercise has been advocated to assist in metabolic control of the nonpregnant diabetic individual, there is a paucity of data about the metabolic effects of exercise during pregnancy. To examine whether moderate exertion may be beneficial in the maintenance of maternal carbohydrate homeostasis, glucose and lactate kinetics were measured in the third trimester in five pregnant nondiabetic women (gestational age, 34.2 ± 0.1 weeks [mean ± SE]) by infusion of 45 μg · kg$^{-1}$ · min$^{-1}$ [6,6-$^{2}H_2$]glucose and 70 μg · kg$^{-1}$ · min$^{-1}$ [U-$^{13}$C]lactate tracers. Subjects were observed at rest for determination of baseline steady-state kinetics over a 30-minute period, and then they exercised for 30 minutes at 60% maximum oxygen consumption ($\dot{V}O_2$max) and were evaluated for 30 minutes postexercise. Glucose and lactate kinetics and lactate oxidation were measured throughout the exercise protocol. This study was repeated postpartum in all individuals at least 6 weeks after delivery. Compared with the steady-state preinfusion period, plasma glucose concentration was not elevated during exercise in either group, nor was plasma lactate concentration significantly different in either group. Glucose kinetics did not change during exercise, but lactate kinetics increased in both groups. $\dot{V}O_2$ and percent of lactate C contribution to $CO_2$, an indication of lactate oxidation, increased proportionally in both groups during exercise. Metabolic perturbations, as measured by glucose and lactate kinetics, do not appear to be different during the third trimester of pregnancy during a relatively short bout of exercise compared with the nonpregnant state.**


GLUCOSE HOMEOSTASIS in pregnancy reflects a unique metabolic milieu involving the relationship between the maternal and fetal-placental units. Utilization of intermittently consumed foodstuffs by the mother is effected by the continuous consumption of energy-producing substrate by the conceptus. Substrate utilization is affected by altered hormonal balance of the gravida, as influenced by the placenta, anterior pituitary, and adrenal cortex.[1-3]

During the last trimester of pregnancy, increased chorionic somatomammotropin (HCS) and prolactin concentrations result in the emergence of insulin resistance with reduced glucose tolerance.[4] Beck and Daughaday[4] and Kaplan et al[5] noted that HCS is diabetogenic and is produced in quantities exceeding any other polypeptide hormone in late pregnancy. Increasing in amount in parallel with an increase in placenta mass, HCS is one of the hormones resulting in "contra-insulin" effects such as persistent glucose production and impaired glucose uptake. These hormones may act to ensure a steady supply of glucose and other substrates to the fetus. Insulin may function as a modifier of their effects on the mother.[6]

Utilization of glucose during exercise increases from seven to 40 times over the level seen during the resting state, depending on exercise intensity.[7,8] Because there is a corresponding increase in the rate of hepatic glucose production, hypoglycemia usually does not occur under normal circumstances.[9] Immediately after the onset of exertion, glucose production increases. During more prolonged exertion, this is followed by mobilization of triglycerides, free fatty acids, and ketones.[10]

The control of glucose homeostasis during exercise has been the subject of numerous studies in the nonpregnant individual.[11-15] A decrease in plasma insulin, an increase in plasma catecholamines, an increase in plasma glucagon, or a combination of these have all been reported to contribute to maintenance of plasma glucose concentration. Others have suggested that insulin plays a central role in the metabolic responses noted.[16] Zinman et al[16] suggested that insulin is important because of its role in the following processes: (1) consumption of glucose by exercising muscle; (2) hepatic production of glucose; and (3) peripheral release of energy substrate.

Exercise has been recommended as a significant factor in the control of hyperglycemia associated with the diabetic state.[17,18] Since the early days following the discovery of insulin, exercise has been advocated as an adjunct in the maintenance of homeostasis.[19] This has been enhanced by the recent interest in exercise by society in general.[20,21] The potential effect of exercise on glucose homeostasis in normal pregnancy is the subject of this investigation.

## SUBJECTS AND METHODS

Five pregnant nondiabetic women between 32 and 35 weeks' gestation were evaluated. They were 29 to 39 years of age and weighed 74.2 ± 7.9 kg (mean ± SE) at the time of study. All women were studied after an overnight fast without prior dietary preparation and after informed written consent had been obtained. The mean hemoglobin $A_{1c}$ level of each patient at the time of the exercise study was 5.7% ± 0.1% (5.3% to 6.1%). All of the patients had a normal 1-hour 50-g oral diabetic screen test or 3-hour 100-g oral glucose tolerance test between 24 and 28 weeks' gestation of their current pregnancy. None of the patients had risk factors for diabetes. They were subsequently studied 6 weeks postpartum (range, 41 to 69 days) as controls.

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### *Study Design*

All patients were fasted for a mean of 10.5 ± 1.1 hours before the study, and the baseline kinetic analysis began 12 to 14 hours after the last evening meal. The patients were acclimated for 30 minutes in a metabolic study room before beginning the study.

Because of the nature of this protocol, the heated-hand technique was not used, but blood was obtained from a free-flowing angiocatheter placed in the antecubital fossa. The opposite extremity was used for delivery of the isotopic tracers. Two samples were taken during a baseline determination of plasma glucose, lactate, insulin, glucagon, and norepinephrine, and the hematocrit, hemoglobin $A_{1c}$, and tracers. The isotopes D-[6,6-$^2H_2$]glucose and [U-$^{13}$C]lactate were infused at rates of 45 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively in 0.9% NaCL following priming infusions of both isotopes. The isotope was infused at 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$ by a Valley Lab 7000 infusion pump (Valley Lab, Boulder, CO). The tracers were infused for 120 minutes before sampling to achieve a baseline steady state. During this period, blood was sampled every 15 to 30 minutes for the first 90 minutes and then every 10 minutes from 90 to 150 minutes. The period from 120 to 150 minutes was considered the baseline steady-state kinetic period. After 150 minutes of isotopic infusion, the patient was seated on a stationary bicycle for 30 minutes of exercise. During this time, samples were taken at 5-minute intervals. Following exercise, the subject remained in the seated position at rest during a 30-minute postexercise period, and samples were taken every 10 minutes. The rates of infusion and concentrations of glucose and lactate infusate were analyzed to determine the actual amount of tracers infused per kilogram per minute. The tracers were obtained from Cambridge Isotope (Woburn, MA) and prepared in stock solutions and tested for sterility and pyrogens (the latter by Ethide Sterilizing, Coventry, RI). The solutions were stored in sterile pharmacy containers and refrigerated at 4°C before use in the study.

Oxygen uptake ($\dot{V}O_2$) was measured by a standard open-circuit spirometric technique[22] using measurement of ambient and expired gas concentrations by a mass spectrometer (MGA 1100; Perkin Elmer, Pomona, CA). Vital signs and oxygen uptake were obtained at 30 and 15 minutes before exercise. Subjects then exercised on a stationary electrically braked cycle ergometer (PedalMate; Collins, Braintree, MA) at a pulse rate consistent with 60% maximal $\dot{V}O_2$ ($\dot{V}O_2$max). $\dot{V}O_2$max had been previously determined by extrapolation of $\dot{V}O_2$ and pulse data from a prior continuous submaximal incremental exercise test to age-specific maximal pulse rates.[23] Exercise was performed at the same intensity for 30 minutes. This was followed by a recovery period of 15 minutes. Power (kilowatts per minute), absolute $\dot{V}O_2$ (liters per minute), relative $\dot{V}O_2$ (liters per kilogram per minute), and pulse (beats per minute) were measured at 10-minute intervals during exertion. The same protocol at the same pedal resistance was performed in postpartum studies in all individuals. Hematocrit was also measured throughout the protocol.

### *Isolation of Plasma Samples*

Plasma was separated by centrifugation at 4°C and stored at −70°C for future analyses. Plasma glucose concentration was determined on a glucose analyzer (model 23A; YSI, Yellow Springs, OH). Plasma insulin concentration was determined by a double-antibody radioimmunoassay using a modification of the method of Hales and Randle.[24] Plasma glucagon was determined by radioimmunoassay using a modification of the method of Faloona and Unger.[25] Plasma norepinephrine concentrations were measured by electrochemical detection.

Blood samples for glucose and lactate kinetic determinations were prepared as follows: For glucose turnover, blood was collected in lithium heparinized tubes and centrifuged to obtain the plasma. Plasma proteins were precipitated with 70% acetone, and the resultant supernate was passed through an anion exchange column (Dowex AG-1-X8; BioRad Laboratories, Melville, NY) and a cation-exchange column (Dowex AG-50-W-X8) and rinsed with $H_2O$ to obtain the neutral fraction containing glucose. The pentacetate derivatives were prepared from the eluent, and $^2H$ enrichment was determined by gas chromatograph–mass spectrometry (GCMS) on a model 5985B GCMS system (Hewlett-Packard, Palo Alto, CA) by electron impact (EI) ionization. For lactate turnover, blood was collected in 3.5% perichloric acid in a ratio of 1:1 and centrifuged to obtained the supernate. The supernate was neutralized with 14% $K_2HCO_3$ and passed through the anion-exchange column (Dowex AG-1-X8), which had been washed with 2N formic acid just before use and rinsed with 2N formic acid. Derivatives were prepared and isotopic enrichment was determined as already described.

### *Calculations*

The turnover rates of glucose and lactate were calculated according to Steele's equations for isotopic non–steady-state conditions.[26] As we have calculated previously,[27]

$$R_A = \frac{F - PV\frac{(G_2 + G_1)}{2}\left(\frac{\Delta E}{\Delta t}\right)}{\left(\frac{E_2 + E_1}{2}\right)},$$

where $R_A$ is the rate of appearance, F is the infusion rate of tracer (micromoles per kilogram per minute), PV is the volume of distribution of glucose, $(G_2 + G_1)/2$ is the mean of plasma glucose measured in two consecutive samples taken at $t_1 + t_2$ (micromoles per liter), $\Delta E$ is the isotopic enrichment of glucose or lactate (mole percent excess), and $\Delta t$ is the time interval $(t_2 - t_1)$ in minutes.

The fraction (F) of lactate C contribution to $CO_2$ was calculated with the equation, $F = (\dot{V}CO_2 \times \%\ [^{13}C]O_2)/(I_A \times 0.99 \times 3)$, where $\dot{V}CO_2$ is the rate of $CO_2$ production (micromoles per kilogram per minute), $\%\ [^{13}C]O_2$ is the percent $^{13}C$ enrichment of expired $CO_2$, $I_A$ is the rate of [U-$^{13}$C]lactate infusion (micromoles per kilogram per minute), and 0.99 is the $^{13}C$ enrichment of lactate.

### *Statistical Analysis*

Statistical analysis was performed using ANOVA with repeated measures. To minimize the probability of a type I error, the $\alpha$ value was set at .0125.

## RESULTS

Subjects demonstrated the same exercise intensity in duplicate exercise tests by several measures. The power produced was 429 ± 39 kilowatts per minute (kpm) in the two exercise tests. Pregnancy versus postpartum values were not significantly different for pulse (136 ± 3 *v* 132 ± 3 beats per minute [bpm]), absolute $\dot{V}O_2$ (1.2 ± 0.1 *v* 1.1 ± 0.1 $L \cdot kg^{-1} \cdot min^{-1}$), or relative $\dot{V}O_2$ (16.9 ± 1.8 *v* 18.5 ± 1.7 $mL \cdot kg^{-1} \cdot min^{-1}$), documenting comparable moderate exercise intensity during both exercise tests.

Figure 1 shows plasma glucose and plasma lactate concentrations for both groups throughout the study. There was no significant elevation of plasma glucose during exercise in the pregnant group (4.88 ± 0.33 *v* 4.22 ± 0.44 mmol/L) or

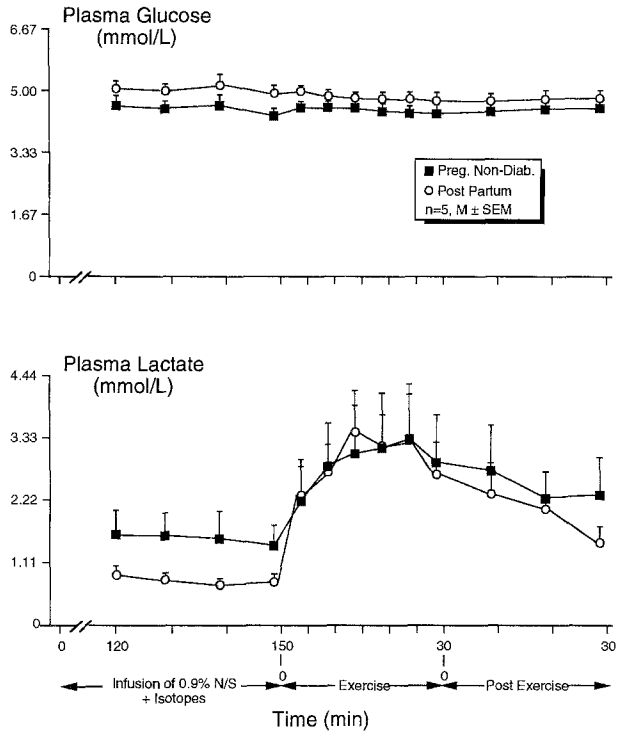


**Fig 1. Plasma glucose and lactate concentrations measured in the third trimester and during the postpartum period.**

the postpartum group (4.92 ± 0.33 *v* 4.94 ± 0.44 mmol/L) as compared with the respective preexercise period.

Plasma lactate concentration was not significantly elevated in the pregnant group (2.89 ± 0.10 *v* 1.67 ± 0.89 mmol/L) or the postpartum group (2.78 ± 1.11 *v* 0.80 ± 0.23 mmol/L) during exercise as compared with the preexercise period.

There was no significant change in plasma insulin concentration in the pregnant group (96.15 ± 43.77 *v* 87.54 ± 52.38 pmol/L) or the postpartum group (65.29 ± 27.27 *v* 66.73 ± 28.70 pmol/L) during exercise as compared with the preexercise period (data not shown).

Plasma glucagon concentration was not significantly elevated in the pregnant group (222 ± 47 *v* 198 ± 64 ng/L) or the postpartum group (144 ± 22 *v* 116 ± 13 ng/L) during exercise as compared with the preexercise period (data not shown).

Pregnant and postpartum groups both had a relatively stable plasma norepinephrine concentration throughout the period preceding exercise. Following initiation of exercise, there was no significant increase in plasma norepinephrine concentration for either group (pregnant, 3.10 ± 1.18 *v* 1.55 ± 0.47 nmol/L; postpartum, 3.51 ± 1.66 *v* 1.35 ± 0.40 nmol/L) (data not shown).

There was no statistical difference in hematocrit values over time for either group (data not shown).

Figure 2 shows the data for glucose kinetic analyses (mole % excess and glucose turnover). During the 30-minute preexercise period, glucose kinetics were stable. There was no significant difference in glucose kinetics during exercise relative to the preexercise period between the pregnant group (21.24 ± 6.12 *v* 8.10 ± 3.46 μmol · $kg^{-1}$ · $min^{-1}$) and the postpartum group (20.68 ± 6.65 *v* 6.17 ± 4.22 μmol · $kg^{-1}$ · $min^{-1}$).

Figure 3 shows the data after lactate kinetic analysis. In the pregnant group, lactate kinetics significantly increased to a maximum of 1.67 ± 0.44 μmol · $kg^{-1}$ · $min^{-1}$ during exercise as compared with the preexercise period (0.44 ± 0.02 μmol · $kg^{-1}$ · $min^{-1}$, $P < .001$). This was similar for the postpartum group (2.90 ± 0.44 μmol · $kg^{-1}$ · $min^{-1}$) during exercise versus the preexercise period (0.44 ± 0.11 μmol · $kg^{-1}$ · $min^{-1}$, $P < .006$).

Figure 4 depicts the values for $\dot{V}CO_2$, atom percent excess, and calculated percent lactate C conversion to $CO_2$. The latter was used as a measure of lactate oxidation. $\dot{V}CO_2$ was higher in the pregnant group during exercise compared with the preexercise period (686.7 ± 22.34 *v* 149.7 ± 20.3 μmol · $kg^{-1}$ · $min^{-1}$, $P < .0001$). The postpartum group had a comparable increase (791.6 ± 318.9 *v* 166.0 ± 27.4 μmol · $kg^{-1}$ · $min^{-1}$, $P < .003$).

There was an increase in lactate C conversion to $CO_2$ during exercise compared with the preexercise period in the pregnant group (79.4% ± 21.1% *v* 25.3% ± 7.3%, $P < .005$; Fig 4). A comparable increase in lactate C conversion to $CO_2$ during exercise compared with the preexercise period was noted in the nonpregnant group (77.2% ± 28.6% *v* 24.1% ± 4.0%, $P < .005$).

## DISCUSSION

Exercise continues to be advocated for the maintenance of health.[21] Specific recommendations have been suggested for pregnancy by means of consensus development.[28] Fetal effects of maternal exertion have been evaluated[29-31] and

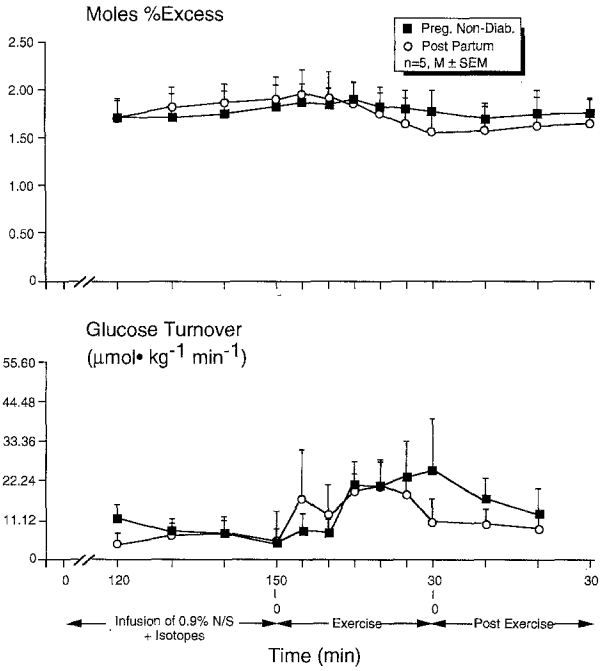


**Fig 2. Mole % excess and glucose turnover measured in the third trimester and during the postpartum period.**

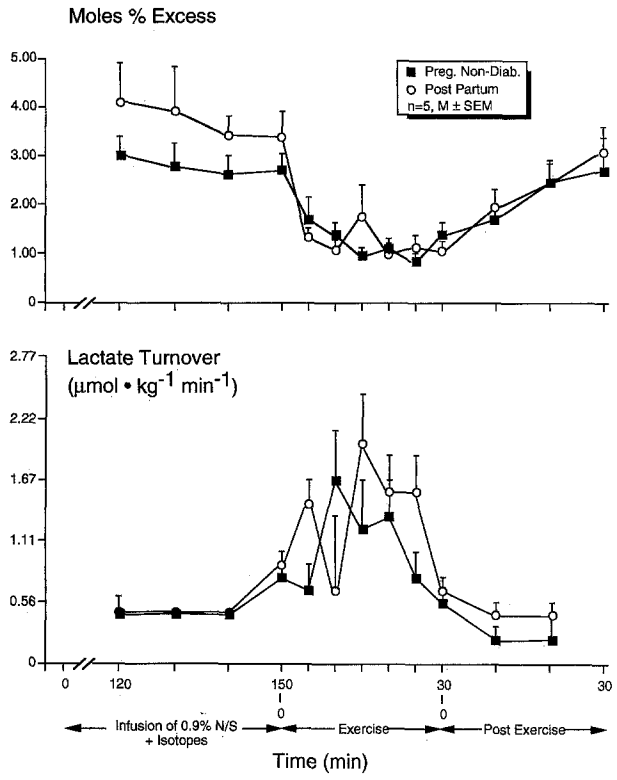


**Fig 3. Mole % excess and lactate turnover measured in the third trimester and during the postpartum period.**

suggest no adverse effects of moderate-intensity exercise over a length of time comparable to our protocol. However, little is known about the metabolic effects of exercise in pregnancy, and no evaluation of glucose and lactate kinetics during exertion has been performed in normal human pregnancy.

Pregnancy induces changes in maternal fuel homeostasis that appear to provide a stable flux of glucose to the developing fetus. The reduction in insulin sensitivity noted in the first and second trimester of normal pregnancy is associated with higher postprandial glucose concentrations, higher fasting free fatty acid concentrations, and a more rapid onset of ketosis. Basal endogenous glucose production appears to be augmented during pregnancy.[32-34] These changes provide the fetoplacental unit with a sustained source of glucose by delivering alternate fuels to maternal tissues.

The adaptive response of maternal fuel homeostasis to fetoplacental requirements may alter the maternal metabolic response to exertion as compared with the postpartum state. During short-term exertion, endocrine responses result in augmented hepatic glucose production, which increases fivefold, effectively maintaining plasma glucose concentration.[7] The hypoinsulinemic effect of exertion may result in more rapid augmentation of hepatic glucose production under conditions of pregnancy-induced insulin resistance. The augmented glucose disposal observed during pregnancy may act in concert with exercise-related augmented muscle glucose uptake to result in greater hepatic production of glucose or possible hypoglycemia at comparable exercise intensity as compared with the postpartum state.

Clapp et al[35] evaluated the changing glycemic response to a short-term bout of exercise during pregnancy to test the hypothesis that pregnancy reverses the nonpregnant hyperglycemic response to sustained exercise. They suggested that the reversal was dependent on the intensity of exercise and was not related to changes in the insulin or catecholamine response to exertion. They speculated that there may be a pregnancy-related decrease in hepatic glucose release and an increase in glucose utilization by muscle during the exercise bout.

Consequently, we examined the effect of pregnancy on maternal glucose production, peripheral glucose concentration, and lactate utilization during exertion by comparing the response in normal pregnancy versus the postpartum state using each patient as her own control. To this end, we chose an exercise intensity known to be free of observable fetal effects but sufficient to produce lactacidemia and relevant endocrine responses. Plasma norepinephrine concentrations of 3.5 mmol/L, mean exercise heart rates of 134

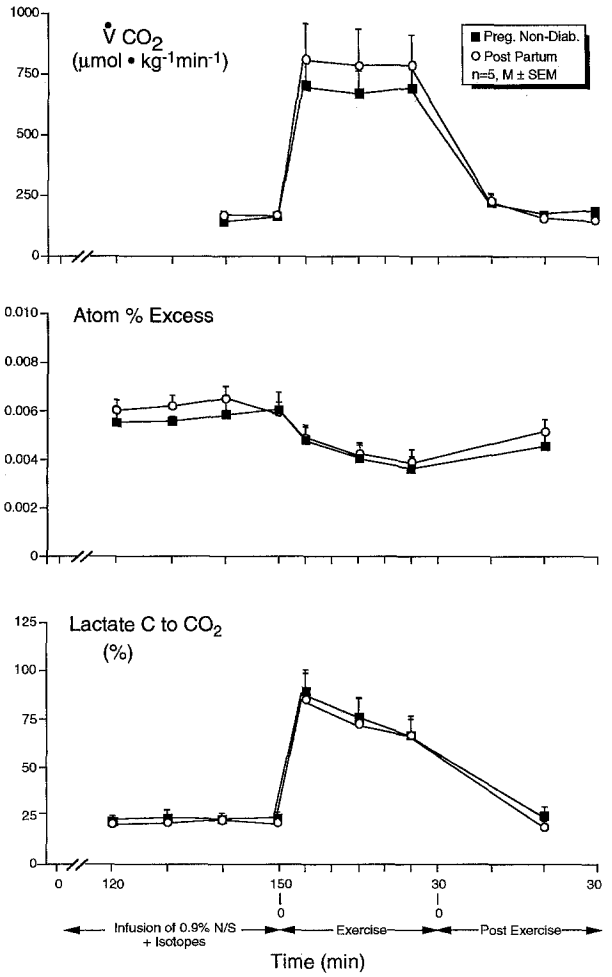


**Fig 4. $\dot{V}CO_2$, atom % excess, and lactate C to $CO_2$ measured in the third trimester and during the postpartum period.**

bpm, and mean exercise $\dot{V}O_2$ rates of 17 mL $\cdot kg^{-1} \cdot min^{-1}$ all support the view that exercise intensities of approximately 60% $\dot{V}O_2$max were achieved.[36,37]

Our data suggest that pregnancy does not affect exercise-induced changes in maternal glucose or lactate kinetics. No significant differences in plasma glucose, the expected increase in glucose production, or the expected increase in lactate concentration induced by maternal exertion were observed in either the pregnant or the postpartum state. This provides confirmatory evidence that carbohydrate levels are maintained in short-term human maternal exertion. Carbohydrate flux to the fetoplacental unit may still be altered by maternal exertion, based on perfusional changes induced by exertion not examined in this study.

Measurement of lactate levels and lactate kinetics continues to be of interest in multiple situations, but is controversial.[38] As noted by Wolfe,[38] there is no net lactate production, because it is essentially a closed pool with connections only to pyruvate. However, lactate levels and lactate kinetics have been of interest to investigators in injured hyperglycemic patients,[39] during exercise,[40] and in the neonate.[41,42] The interest relative to exercise has been an important topic of discussion for many years. It has been pointed out that exercise is the physiological aberration that most significantly affects lactate metabolism (concentration and kinetics). It has been suggested that the metabolism of lactate is a function of exercise intensity rather than of the amount or duration of exercise, and is inversely a function of an individual's aerobic oxidative capacity, or $\dot{V}O_2$max. Or, as more recently discussed, lactate concentration during incremental exercise does not necessarily indicate muscle lactate production.[43] It more likely reflects the difference between the release of lactate from muscle and the uptake by various organs, and may be a useful measure for predicting performance. Our data can be evaluated in this light, and can be interpreted to suggest that there is apparently both increased production and utilization, which is expected. However, at the level of intensity measured in our subjects, there are no differences between the pregnant and the postpartum state.

Furthermore, despite evidence that these subjects exercised at moderate intensity, this exercise protocol did not produce the expected decrease in plasma insulin concentration nor an increase in glucagon concentration. Consequently, our observation of unaltered glycemia and no pregnancy effects on lactate concentration cannot be extrapolated to more intense or prolonged exertion, during which pregnancy might be found to have an effect on carbohydrate homeostasis. Our data suggest that the pregnant nondiabetic woman has metabolic responses comparable to those in brief, moderately intense exercise in the third trimester of pregnancy as compared with the nonpregnant state.

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