Cardiovascular Function Before, During, and After the First and Subsequent Pregnancies

James Ford Clapp III, MD, and Eleanor Capeless, MD

This study was designed to test the hypothesis that the vascular remodeling of pregnancy begins early, persists for at least 1 year after delivery, and is accentuated by a second pregnancy. Serial estimates of heart rate, arterial pressure, left ventricular volumes, cardiac output, and calculated peripheral resistance were obtained before pregnancy, every 8 weeks during pregnancy, and 12, 24, and 52 weeks postpartum in 15 nulliparous and 15 parous women using electrocardiography, automated manometry, and M-mode ultrasound. During pregnancy, body weight increased 14.5 ± 1.8 kg and returned to prepregnancy values 1 year postpartum. Heart rate peaked at term 15 ± 1 beat/min above prepregnancy levels (57 ± 1 beat/min). Mean arterial pressure reached its nadir (−6 ± 1 mm Hg) at 16 weeks, returning to baseline at term. The increases in left ventricular volumes and cardiac output (2.2 ± 0.2 L/min) peaked at 24 weeks as did the 500 ± 29 dynes·cm·s^{-5} decrease in peripheral resistance, and their magnitude was significantly greater in the parous women. Postpartum they gradually returned toward baseline but remained significantly different from prepregnancy values in both groups at 1 year. We conclude that cardiovascular adaptations to the initial pregnancy begin early, persist postpartum, and appear to be enhanced by a subsequent pregnancy. We speculate that persistence of these changes may lower cardiovascular risk in later life. ©1997 by Excerpta Medica, Inc.

(Am J Cardiol 1997;80:1469–1473)

In rodents, sheep, and humans, pregnancy is associated with both structural and functional changes in the heart and vessels.[1–7] Ventricular dimensions, heart rate, cardiac output, vascular compliance, and capacitance increase, peripheral resistance, and blood pressure decrease. Many of these changes can be induced by hormonal administration[8–10] and appear to be normally induced by the hormonal milieu of pregnancy which influences vessel structure, basal tone, and reactivity[7,11–13] via receptors for chorionic gonadotropin, estradiol, and progesterone located in vascular endothelium and smooth muscle.[14,15] Serial studies in humans suggest that these changes occur early in the course of pregnancy and that they persist for an unknown period of time postpartum.[5–7,10,11,16,17] However, there is little information on the duration and magnitude of these changes postpartum, the effects of subsequent pregnancy on their magnitude, or their effect on long-term cardiovascular benefit or risk.[17–19] The current study was designed to explore these issues by testing the hypothesis that the vascular remodeling of pregnancy begins early, persists for at least 1 year after delivery, and is accentuated by a second pregnancy.

From the Departments of Reproductive Biology and Obstetrics and Gynecology, Case Western Reserve University and MetroHealth Medical Center, Cleveland, Ohio; and the Department of Obstetrics and Gynecology, University of Vermont College of Medicine, Burlington, Vermont. This study was supported by National Institutes of Health Grants HD11089, HD21268, and RR00080, Bethesda, Maryland; and funds from MetroHealth Medical Center, Cleveland Ohio, and the Alexander von Humboldt Foundation, Bonn, Germany. Manuscript received April 15, 1997; revised manuscript received and accepted September 8, 1997.

Address for reprints: James F. Clapp III, MD, Department of Obstetrics and Gynecology, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland Ohio 44109.

METHODS

Study group: Thirty, healthy, physically active, nonsmoking women were recruited before pregnancy and studied serially before, during, and for 1 year after a clinically normal, singleton pregnancy. Fifteen were nulliparous and 15 were parous (1 or 2 previous pregnancies) at the time of enrollment. All delivered at term, breast fed for 3 to 9 months, and used barrier forms of contraception. The protocol was approved by the institutional review committees and all subjects gave informed consent at the time of enrollment. Some of the data obtained in 4 subjects have been previously reported.[6,17]

Study design: After initial evaluation, a mock set of measurements was obtained to acquaint each subject with the equipment and procedures. Thereafter, serial estimates of heart rate, arterial pressure, and left ventricular volumes were obtained under standardized conditions before pregnancy, every 8 weeks during pregnancy, and 12, 24, and 52 weeks postpartum (±1 week). Cardiac output and systemic vascular resistance were calculated from these data. Data were not normalized for body surface area or weight because the former cannot be accurately estimated during pregnancy and the latter does not accurately reflect changes in lean body mass during pregnancy.[20] Outcome parameters were analyzed using repeated-measures analysis of variance to detect significant changes over time in the entire group and within each group. Significant within group and group differences between individual time points were also examined post hoc using a paired *t* test. Between-group differences at each time point were detected using the unpaired *t* test. The level of significance was set at a p value ≤ 0.05 and all data are presented as mean ± SEM.

TABLE I Serial Cardiovascular Data for 30 Subjects

Time (wks)	Heart Rate (beats/min)	Mean Pressure (mm Hg)	End-Diastolic Volume (ml)
Before pregnancy	57 ± 1	84 ± 1	123 ± 3
8 wks pregnant	64 ± 2*	80 ± 2*	133 ± 4*
16 wks pregnant	67 ± 1*	78 ± 1*	137 ± 4*
24 wks pregnant	69 ± 1*	78 ± 1*	142 ± 4*
32 wks pregnant	71 ± 1*	80 ± 1*	141 ± 4*
38 wks pregnant	72 ± 2*	82 ± 2	140 ± 4*
12 wks postpartum	60 ± 1	83 ± 1	138 ± 4*
24 wks postpartum	58 ± 1	84 ± 1	133 ± 4*
52 wks postpartum	58 ± 2	82 ± 2	132 ± 4*

*Significantly different from before pregnancy ($p < 0.05$).
Data are expressed as mean ± SEM.

TABLE II Serial Cardiovascular Data for 30 Subjects

Time (wks)	Stroke Volume (ml)	Cardiac Output (L/min)	Vascular Resistance (dynes·cm·sec^{-5})
Before pregnancy	82 ± 2	4.69 ± 0.24	1,428 ± 30
8 wks pregnant	92 ± 3*	5.90 ± 0.26*	1,080 ± 27*
16 wks pregnant	94 ± 3*	6.31 ± 0.24*	984 ± 31*
24 wks pregnant	97 ± 3*	6.72 ± 0.29*	928 ± 28*
32 wks pregnant	96 ± 3*	6.80 ± 0.28*	935 ± 26*
38 wks pregnant	96 ± 3*	6.91 ± 0.30*	946 ± 37*
12 wks postpartum	94 ± 3*	5.65 ± 0.24*	1,175 ± 32*
24 wks postpartum	90 ± 2*	5.22 ± 0.23*	1,289 ± 28*
52 wks postpartum	89 ± 2*	5.19 ± 0.21*	1,276 ± 27*

*Significantly different from before pregnancy ($p < 0.05$).
Data are expressed as mean ± SEM.

TABLE III Cardiovascular Data by Parity

Time (wks)	End-Diastolic Volume—First Pregnancy (ml)	End-Diastolic Volume—Second Pregnancy (ml)	Stroke Volume—First Pregnancy (ml)	Stroke Volume—Second Pregnancy (ml)
Before pregnancy	123 ± 5	122 ± 5	84 ± 5	80 ± 4
8 wks pregnant	131 ± 5	135 ± 5	90 ± 4	93 ± 4
16 wks pregnant	134 ± 5	139 ± 5	92 ± 4	96 ± 2
24 wks pregnant	138 ± 5	145 ± 5	94 ± 4	100 ± 3
32 wks pregnant	137 ± 5	145 ± 5	92 ± 4	100 ± 2*
38 wks pregnant	138 ± 5	143 ± 5	93 ± 4	99 ± 4
12 wks postpartum	135 ± 5	141 ± 5	91 ± 4	97 ± 3
24 wks postpartum	129 ± 5	138 ± 5	88 ± 4	95 ± 3
52 wks postpartum	129 ± 5	135 ± 5	88 ± 4	92 ± 3

*Indicates a significant between-group difference, ($p < 0.05$).
Data are expressed as mean ± SEM.

Specific methodology: Measurements were obtained in a relaxed atmosphere by familiar personnel. After instrumentation, the subject rested in the left lateral decubitus position for 20 to 30 minutes and then serial estimates of heart rate, blood pressure, and left ventricular end-diastolic and end-systolic dimensions were obtained over 10 to 15 minutes without positional change. Systolic and diastolic blood pressure (3rd Korotkoff sound) were estimated every 1 to 2 minutes on the right arm using either a mercury manometer or a Colin APPM 630 portable monitor (San Antonio, Texas) in the auscultory mode. The calibration of the latter was routinely checked against a mercury manometer after application to the subject and results corrected for the zero offset created by the left lateral position. Mean arterial pressure was calculated as diastolic blood pressure plus 1/3 of the pulse pressure. Left ventricular dimensions were repeatedly estimated by 1 of 3 examiners with M-mode ultrasound via a left parasternal long-axis view of the left atrium, left ventricle, and ascending aorta using either a GE 3600 (Milwaukee, Wisconsin), an ATL Ultramark 4 (Bothell, Washington), or a Siemens sonoline SL2 (Frankfurt, Germany). All studies on an individual subject were obtained using the same machine and, in all but 3 cases, by the same examiner.

The M-mode tracing and measurements of the left ventricular end-systolic and end-diastolic dimensions were obtained in accordance with the guidelines published by the American Society of Echocardiography.[21] Over the 10- to 15-minute study interval, a minimum of 9 and a maximum of 21 separate estimates were obtained at various phases of the respiratory cycle, and the average values obtained were used to calculate left ventricular end-diastolic and end-systolic volumes using the formula developed by Teichholtz for a modified prolate ellipsoid.[22] This formula has been validated against angiography and thermodilution in nonpregnant individuals.[22,23] The value obtained using it with M-mode alone during pregnancy is similar to that obtained with Doppler and M-mode, which has been validated against thermodilution in pregnant women.[5,24] The within-study variability of the individual measurements around the mean averaged ± 5%, with individual differences ranging from 0% to 14%. Heart rate was measured at the same time as the ventricular dimensions from the electrocardiogram or the ultrasound trace. These data were used to calculate stroke volume (end diastolic − end-systolic volume), cardiac output (stroke volume × heart rate), and systemic vascular resistance without correction for central venous pressure (mean arterial pressure/cardiac output × 80).[6]

RESULTS

Subject characteristics: The subjects all were in good health, and, on the basis of education (18 ± 1 year) and income (upper 2 quartiles for state and county of residence), were classified as coming from the middle and upper socioeconomic class. Most (26 of 30) exercised regularly before, during, and after their pregnancy. They were 32 ± 1 years of age, weighed 61.0 ± 1.8 kg before pregnancy, and returned to that weight by 1 year after delivery (61.6 ± 1.8 kg). Their prepregnancy percent body fat, estimated from 5 site skinfolds,[11] averaged 18.4 ± 2.0% and their pregnancy weight gain 14.5 ± 1.6 kg. The women in the nulliparous and multiparous groups were similar in age (31 ± 1 vs 32 ± 1 years), height (168 ± 3 vs 167 ± 3 cm), prepregnancy weight (60.6 ± 2.3 vs 62.1 ± 2.8 kg), and prepregnancy percent body fat

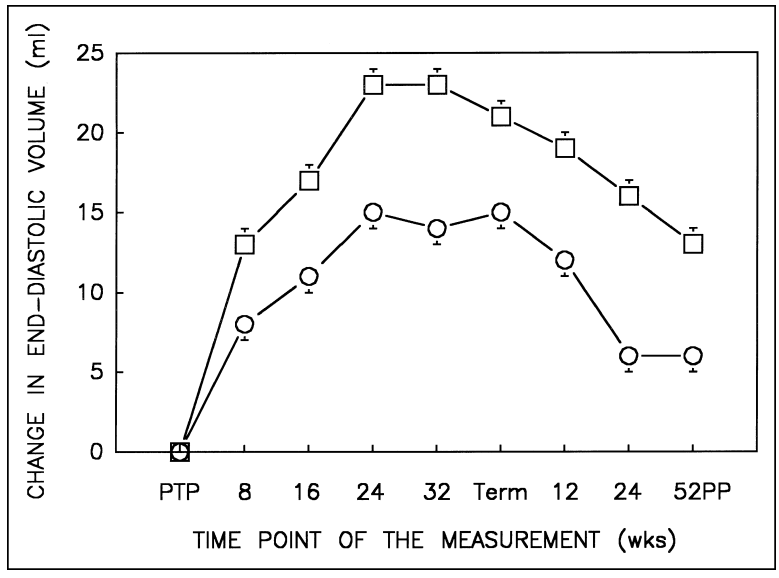

FIGURE 1. Change in left ventricular end-diastolic volume during normal pregnancy and the first year postpartum in nulliparous and parous women. *Open circles,* 15 nulliparous women; *open squares* 15 parous women. Data are presented as mean ± SEM. The rate of change is significantly different in the 2 groups through the 24th week and the magnitude of the change is significantly greater in the parous group at all time points other than before pregnancy (PTP).

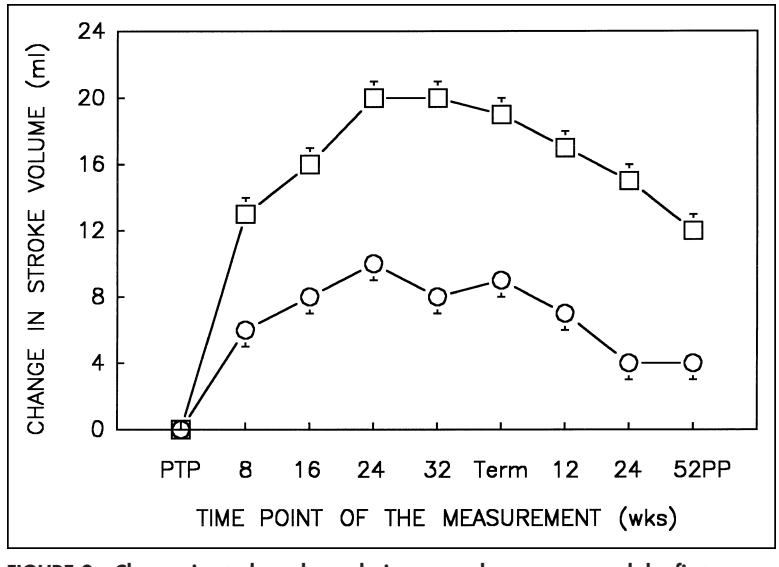

FIGURE 2. Change in stroke volume during normal pregnancy and the first year postpartum in nulliparous and parous women. *Open circles,* 15 nulliparous women; *open squares,* 15 parous women. Data are presented as mean ± SEM. The rate of change is significantly different in the 2 groups through the 24th week and the magnitude of the change is significantly greater in the parous group at all time points other than before pregnancy (PTP).

(18.2 ± 2.2% vs 18.6 ± 2.4%). Pregnancy weight gains were also similar (15.0 ± 2.0 vs 13.9 ± 1.9 kg), and weights in both groups had returned to prepregnancy levels at 1 year postpartum (61.1 ± 2.4 vs 62.3 ± 2.7 kg).

Cardiovascular measurements in the entire study group: The serial estimates of heart rate, mean arterial blood pressure, left ventricular end-diastolic volume, stroke volume, cardiac output, and calculated systemic vascular resistance for the entire study group are detailed in Tables I and II. Note that heart rate increased early, peaked at term 15 beats/min above prepregnancy levels, returned to baseline by 12 weeks postpartum, and remained at that level throughout the first year postpartum. Mean arterial pressure decreased early, reaching its nadir by the 16th week, and returned to prepregnancy values at term with no significant change thereafter. Left ventricular end-diastolic and stroke volumes also increased steeply at 8 and 16 weeks and then abruptly leveled off with no further significant changes after the 24th week. Although both gradually returned toward prepregnancy levels postpartum, both remained significantly above prepregnancy levels throughout the first year after delivery. As a result of these changes, a similar time course was observed for the changes in cardiac output and systemic vascular resistance. Over 70% of the increase in cardiac output and >85% of the decrease in systemic vascular resistance occurred by the 16th week and there were no further significant changes in either parameter after the 24th week. Likewise, 23% of the pregnancy-associated increase in cardiac output and 30% of the pregnancy-associated decrease in systemic vascular resistance were still present 1 year postpartum. Ejection fraction was unchanged throughout.

Cardiovascular measurements based on parity: Parity had no significant effect on either the time course or magnitude of the pregnancy-associated changes in heart rate and arterial blood pressure (data not shown), and the same was true for the absolute values for left ventricular end-diastolic volume and stroke volume (Table III). However, the absolute changes in left ventricular end-diastolic volume and stroke volume increased significantly faster until the 24th week, and were significantly greater in magnitude in women experiencing their second or third pregnancy at all time points (Figures 1 and 2). As a result, the absolute changes in cardiac output and systemic vascular resistance were significantly different between the 2 groups at many time points (Table IV) and, save for systemic vascular resistance 1 year postpartum, the absolute changes for both were significantly different throughout (Figures 3 and 4).

DISCUSSION

To the best of our knowledge, this study is the first that has prospectively assessed the serial changes in

TABLE IV Cardiovascular Data by Parity

Time (wks)	Cardiac Output—First Pregnancy (L/min)	Cardiac Output—Second Pregnancy (L/min)	Vascular Resistance—First Pregnancy (dynes·cm·sec^{-5})	Vascular Resistance—Second Pregnancy (dynes·cm·sec^{-5})
Before pregnancy	4.76 ± 0.28	4.64 ± 0.20	1,418 ± 50	1,436 ± 58
8 wks pregnant	5.54 ± 0.34	6.36 ± 0.34*	1,157 ± 35	993 ± 41*
16 wks pregnant	6.03 ± 0.26	6.59 ± 0.33	1,032 ± 30	951 ± 29*
24 wks pregnant	6.25 ± 0.33	7.19 ± 0.37*	991 ± 36	886 ± 39*
32 wks pregnant	6.52 ± 0.38	7.27 ± 0.38	963 ± 37	894 ± 41
38 wks pregnant	6.49 ± 0.43	7.50 ± 0.36*	988 ± 42	901 ± 39
12 wks postpartum	5.34 ± 0.29	5.96 ± 0.29	1,236 ± 51	1,142 ± 53
24 wks postpartum	4.95 ± 0.31	5.66 ± 0.21*	1,327 ± 52	1,193 ± 41*
52 wks postpartum	5.05 ± 0.29	5.39 ± 0.26	1,272 ± 42	1,236 ± 43

*Indicates a significant between-groups difference, ($p < 0.05$).
Data are expressed as mean ± SEM.

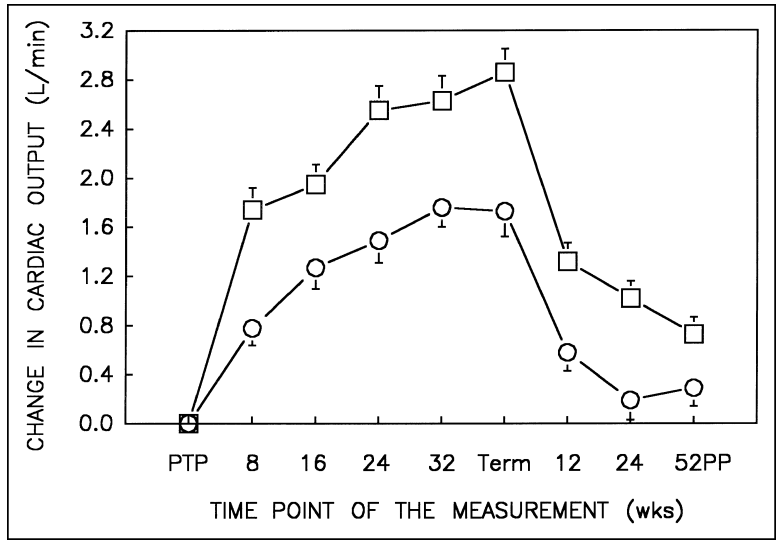

FIGURE 3. Change in cardiac output during normal pregnancy and the first year postpartum in nulliparous and parous women. *Open circles,* 15 nulliparous women; *open squares,* 15 parous women. Data are presented as the mean ± SEM. The rate of change is significantly different in the 2 groups through the eighth week and the magnitude of the change is significantly greater in the parous group at all time points other than before pregnancy (PTP) and 52 weeks postpartum (52PP).

central cardiovascular function in healthy women before, during, and for a protracted period of time after pregnancy. The data confirm earlier findings indicating that the cardiovascular changes of pregnancy begin early and are largely completed in the first half of pregnancy.[1,5–7,11] Second, the consistent differences seen in the magnitude of the absolute changes in the parous group indicate that ventricular volumes, cardiac output, and systemic resistance are greater during subsequent pregnancies in physically active women. Finally, these changes do not return to prepregnancy levels for at least 1 year after delivery in women who both breast feed and remain physically active.

The latter 2 findings are new. The first suggests that the hormonal stimulus provided by the initial pregnancy imprints the vasculature in a way that alters the magnitude of the cardiovascular response to subsequent hormonal stimulation. To date no other study has addressed the effect of parity on the magnitude of the pregnancy-associated changes in ventricular volume, cardiac output, and systemic resistance, but the observations of Hart et al,[25] indicating that aortic size and compliance is greater in parous women, suggest that it is real. This raises the issue of the significance of parity as a determinant of cardiovascular risk later in life. Theoretically, these pregnancy-related changes reflect a hyperdynamic, compliant circulatory system that should decrease barotrauma over extended periods of time and thereby reduce cardiovascular risk in a similar fashion to that produced by regular exercise and postmenopausal estrogen replacement therapy.[26–28] The epidemiologic data addressing this issue have recently been reviewed in detail by Ness et al.[18] They conclude that multiple confounders cloud the issue, but that multiparity (≥4 live births) with all its accompanying confounders (stress, socioeconomic status, weight gain, fat mass, lipid profile, and so forth) is associated with a modest increase in cardiovascular risk later in life. Likewise, a recent study by Sadaniantz et al.[19] found no consistent relation between multiparity and left ventricular volumes or improved cardiovascular function in sedentary women an average of 12 years after their last pregnancy, indicating that these changes do not persist into the perimenopausal years in a sedentary populace. Unfortunately, there are no data addressing the effect of 1 or 2 pregnancies in physically active women on either long-term cardiovascular function or risk. Additional studies addressing the long-term effects of this combination would be of interest.

The second new finding extends earlier observations[5,16,17,25] and indicates that the vascular remodeling of pregnancy persists for an extended period of time in healthy active women. Indeed, it is possible that these women's regular exercise programs poten-

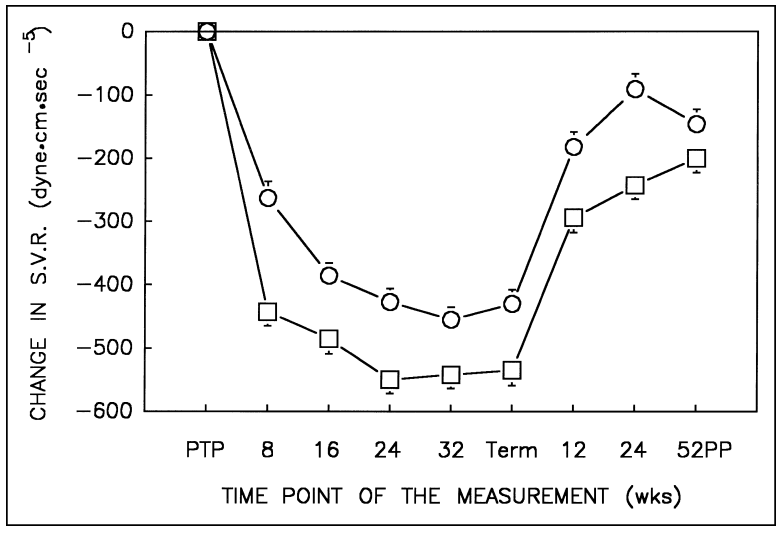

FIGURE 4. Change in systemic vascular resistance (S.V.R.) during normal pregnancy and the first year postpartum in nulliparous and parous women. *Open circles* 15 nulliparous women; *open squares,* 15 parous women. Data are presented as mean ±SEM. The rate of change is significantly different in the 2 groups through the eighth week and the magnitude of the change is significantly greater in the parous group at all time points other than before pregnancy (PTP). 52PP = 52 weeks postpartum.

tiated the changes as does the similar effects of physical training alone on left ventricular volumes.[26] Indeed, the combined effects of pregnancy and regular exercise on ventricular function may help to explain the increased maximal oxygen consumption that has been documented in female runners who have exercised regularly during and after pregnancy.[29] Also, breast feeding, through its effects on blood volume,[30] may have played a role.

Finally, in this physically active group, the 2.3-L increase in cardiac output was due to a 17% increase in stroke volume and a 26% increase in heart rate. Published reports indicate that these percentages are quite sensitive to changes in position (left lateral, supine, upright), which alter preload, and that they also are highly variable between women. The latter probably reflects differences in fitness, which alter baseline nonpregnant values.[26] In this relatively fit group, baseline heart rates were low and stroke volumes were high. In a sedentary populace with the same cardiac output, baseline heart rate would be higher (about 69 beats) and baseline stroke volume lower (about 68 ml). In those women, the same pregnancy-associated incremental changes would probably occur, but the percent increase in the 2 components would be more balanced (i.e., a 21% increase in stroke volume and a 22% increase in heart rate).

Acknowledgment: We wish to thank Karen H. Risk, Sarah Appleby-Wineberg, Mary Kortan, and Beth Lopez for there expert assistance in conducting these studies.

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