Cardiac output increases independently of basal metabolic rate in early human pregnancy

M. E. A. SPAANDEMAN, M. MEERTENS, M. VAN BUSSEL, T. H. A. EKhart, AND L. L. H. PEETERS
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Spaannderman, M. E. A., M. Meertens, M. Van Bussel, T. H. A. Ekhart, and L. L. H. Peeters. Cardiac output increases independently of basal metabolic rate in early human pregnancy. Am J Physiol Heart Circ Physiol 278: H1585–H1588, 2000.—Early pregnancy is characterized by the institution of a high-flow low-resistance circulation. In this study, we tested the hypothesis that these hemodynamic changes develop independently of changes in basal metabolic rate. In 12 healthy women, we determined and calculated once during the follicular phase (day 5 ± 2) and at 6, 8, 10, and 12 wk of pregnancy the following variables: body weight and length, body mass index, fat-free mass (FFM), mean arterial pressure (MAP), heart rate (HR), stroke volume, cardiac output (CO), total peripheral vascular resistance (TPVR), resting energy expenditure (REE), FFM REE (REEFFM), and respiratory quotient (RQ). At 6 wk of gestational age, HR and CO had increased, whereas MAP and TPVR had decreased. These changes persisted throughout the study period. Meanwhile, REE, REEFFM, RQ, FFM, and body weight did not change consistently. The changes with pregnancy in hemodynamics did not correlate with those in basal metabolic rate. In early pregnancy, the institution of a high-flow low-resistance circulation develops without a concomitant rise in basal metabolic rate. These findings support the concept that the hemodynamic changes in early pregnancy develop independently of concomitant changes in basal metabolic rate.

In pregnancy, systemic arterial vasodilation represents one of the first detectable changes in systemic hemodynamics. This vasodilation then initiates a cascade of compensations in the circulation and volume homeostasis that include, among others, a rise in cardiac output (CO), hemodilution, and activation of the renin-angiotensin-aldosterone system (6, 8, 11–13, 21). Neither the mechanism responsible for the initial hemodynamic change in early pregnancy nor its functional meaning in this period of pregnancy is understood. Insight in the interrelation between the early pregnancy increase in CO and a concomitant change in metabolic rate would improve our understanding of the mechanism and functional meaning of the early pregnancy vasorelaxation. Although in late pregnancy basal metabolism is elevated, the available data on change in metabolic rate in early pregnancy are scarce and inconclusive (4, 9, 19, 20). Moreover, to the best of our knowledge, the metabolic rate in early pregnancy has never been measured simultaneously with CO in a longitudinal study. Therefore, it is still obscure whether or not CO increased before or after a rise in metabolic rate in the first trimester of pregnancy.

The objective of the present study was to test the hypothesis that, in early pregnancy, the CO increases independently of concomitant changes in metabolic rate. To this end, we serially measured blood pressure, CO, and resting energy expenditure in 12 women during the follicular phase of the menstrual cycle and in subsequent early pregnancy.

METHODS

Selection and Patient Characteristics

In this study, 12 nonsmoking healthy women were enrolled. Participants were recruited by advertisement. None of the women used oral contraceptives or other medication. Measurements were performed in the follicular phase (FP; day 5 ± 2) and at 6, 8, 10, and 12 wk of pregnancy. The gestational age at the time of measurement was verified by ultrasound biometry of the embryo (series 150; Pie Medical, Maastricht, The Netherlands) before the first measurement session in pregnancy. Gestational age was blinded for the individuals who determined metabolic and hemodynamic parameters.

Experimental Procedure

Metabolism. After participants fasted overnight, each experimental session was started with the measurement of fat-free mass (FFM, kg) and resting energy expenditure (REE, kcal/24 h). Mean arterial blood pressure (MAP, mmHg) and heart rate (HR, beats/min) were recorded intermittently throughout the measurement session by a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL). FFM was determined by bioelectrical impedance (BIA-101; RJL Systems, Detroit, MI), a method associated with 0.3-kg variation between consecutive days (22). REE, which comprises the sleeping metabolic rate supplemented with the energy cost of being awake, was determined by indirect calorimetry using a computerized open-circuit ventilated hood system (Oxycon B; jaeger, Breda, The Netherlands). In a horizontal position, each participant breathes inside a canopy that forms a gas-tight barrier between the room air and the respirable air. Using a continuous inflation and suction pump, a constant flow of exhaled air and room air is drawn from and to the canopy. The gas composition...
and the velocity of the air flow are measured at the outlet of the air suction pump. In steady state, differences in gas composition between the canopy and room air vary as a function of the oxygen consumption ($\dot{V}O_2$, l/min) and carbon dioxide production ($\dot{V}CO_2$, l/min; see Ref. 23). From these values, the respiratory quotient (RQ) was calculated according to the formula

$$RQ = \frac{\dot{V}CO_2}{\dot{V}O_2}$$

Twenty-four-hour REE is calculated using the abbreviated Weir formula (25) and is expressed as kilocalories per 24 h and kilocalories per 24 h per kilogram FFM

$$REE = \frac{(3.9 + 1.1RQ) \times \dot{V}O_2 \times 1,440}{FFM}$$

$$REE_{FFM} = \frac{(3.9 + 1.1RQ) \times \dot{V}O_2 \times 1,440}{CO \times FFM}$$

where $REE_{FFM}$ is FFM REE. In our laboratory, the determination of RQ and that of REE has an intraindividual coefficient of variation of 6 and 1.2%, respectively (23).

Hemodynamics. Echocardiography to assess CO was performed in a semiled lateral position, immediately after completion of the REE measurement after ~5 min of rest, using a cross-sectional, phased-array echocardiographic Doppler system (Hewlett-Packard Sonos 2000 and 2500; see Ref. 12). CO was calculated according to the formula

$$CO (l/min) = \text{stroke volume} \times HR$$

In this formula, HR was obtained by taking the mean of five consecutive R-R intervals on the electrocardiogram. Stroke volume (SV, ml) was calculated by multiplying the aortic velocity integral and the aortic area. Aortic flow was measured across the aortic valves from an apical approach. SV was calculated using the average area under the aortic velocity curve (aortic velocity integral) of five consecutive ejections. Aortic valve diameter necessary for the calculation of the aortic area was measured during systole by M mode, off-line and at the orifice. Total peripheral vascular resistance (TPVR) was calculated as follows

$$TPVR (\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}) = 80 \times \frac{\text{MAP}}{\text{CO}}$$

The value used for MAP was obtained during the CO measurement and was calculated as the mean of three consecutive recordings.

### Table 1. Demographic data (follicular phase)

| Age, yr | 29 ± 3 |
| Height, cm | 168 ± 7 |
| BMI, kg/m² | 23 ± 3 |
| Parity, % nulliparous | 50 |
| MAP, mmHg | 91 ± 12 |

Values are means ± SD. BMI, body mass index; MAP, mean arterial pressure.

Statistical Analysis

Data are presented as means ± SD unless otherwise stated. Differences relative to the value obtained during the FP were evaluated with ANOVA for repeated measures. Correlations between concomitantly measured variables in the different phases were tested by Spearman’s rank correlation analysis. A P value <0.05 was considered statistically significant.

### RESULTS

The demographic characteristics of the participants are listed in Table 1. In all subjects, the course of pregnancy was uneventful.

REE, $REE_{FFM}$, and RQ did not change consistently in the study period between the FP and the 12th wk of pregnancy (Table 2). Body weight and FFM varied little and inconsistently between the five measurement sessions. Meanwhile, CO and HR had increased, and TPVR and MAP had decreased consistently in the study period, a change already noticed by the 6th wk (Table 3 and Fig. 1).

The CO per unit REE and per unit $REE_{FFM}$ increased significantly over the study period ($P = 0.04$, $r = 0.90$, $r^2 = 0.80$ and $P = 0.02$, $r = 0.94$, $r^2 = 0.89$, respectively). Within one measurement session, HR did not change appreciably between the period of REE measurement and the subsequent period of CO determination.

Neither the change in REE nor that in $REE_{FFM}$ in the course of the five measurement sessions correlated with the observed concomitant changes in CO ($r = -0.29$, $r^2 = 0.09$ and $r = -0.44$, $r^2 = 0.19$, respectively).

### DISCUSSION

Early pregnancy is characterized by the development of a high-flow low-resistance circulation (6, 7, 9, 12, 13, 21). However, at present, the exact mechanism responsible for this effect is still obscure. A rise in metabolic rate could be one of the possible triggers for these circulatory adjustments. Conversely, when the metabolic rate does not increase, the high-flow low-resistance circulation is associated with a CO rise in excess of metabolic demands. In this study, we explored the possible interrelationship between systemic vasorelaxation and metabolic rate in 12 healthy women by measuring CO together with REE during five consecutive sessions in the 1st wk of pregnancy when hemodynamic changes are the largest. In our study, the institution of a high-flow low-resistance circulation in early...
pregnancy develops without a concomitant rise in basal metabolic rate.

Reports on REE in early pregnancy are rather conflicting, with some studies reporting an increment and others a fall in basal metabolic rate in early pregnancy (9, 20). Some of these differences can be explained by the methods employed, the procedure used to standardize measurement conditions, and the role of fat mass with REE. In fact, suppression of REE in early pregnancy is mainly observed in women with a low body mass index, and also, in advanced pregnancy, the largest increase in REE occurs in women with the highest body mass indexes (4, 20). During the first 12 wk of pregnancy, we did not find an appreciable change in REE and RQ. Conversely, the concomitantly measured CO had already increased by the 6th wk of pregnancy. Meanwhile, the time-dependent change in CO and that in REE did not correlate. Also, the per unit REE and REE\textsubscript{FFM} was found to increase with advancing amenorrhea. All of these phenomena support the development of a hyperdynamic circulation in the first weeks of pregnancy. To maintain the balance in Starling forces within the capillary bed, the institution of a hyperdynamic circulation should be paralleled by a fall in arteriovenous oxygen difference over the first weeks of pregnancy (10, 15). This indicates that neither trophoblastic hormones in ovariectomized rats to a level observed in normal rat pregnancy (1, 3, 24). Moreover, although not found by all investigators, suppletion of sex steroid hormones in ovariectomized rats to a level observed in pregnancy can alter vascular sensitivity to vasodilatory stimuli in a manner comparable to that seen in normal pregnancy (10, 15). This indicates that neither trophoblastic hormones nor the placenta itself is needed to induce these hemodynamic changes.

In conclusion, early pregnancy is characterized by the development of a hyperdynamic circulation. This adaptive change seems to be the result of a primary relaxation of the arterial vasculature together with the opening of protective arteriovenous shunts.

Table 3. Hemodynamic data

<table>
<thead>
<tr>
<th></th>
<th>Follicular</th>
<th>6 Wk</th>
<th>8 Wk</th>
<th>10 Wk</th>
<th>12 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>66 ± 5</td>
<td>72 ± 5\textsuperscript{*}</td>
<td>70 ± 6\textsuperscript{*}</td>
<td>67 ± 8</td>
<td>71 ± 7\textsuperscript{*}</td>
</tr>
<tr>
<td>SV, ml</td>
<td>79 ± 7</td>
<td>85 ± 12</td>
<td>85 ± 12</td>
<td>84 ± 11</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.2 ± 0.6</td>
<td>6.0 ± 0.7\textsuperscript{*}</td>
<td>5.9 ± 1.0\textsuperscript{*}</td>
<td>5.8 ± 0.8\textsuperscript{*}</td>
<td>6.1 ± 0.4\textsuperscript{*}</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92 ± 11</td>
<td>87 ± 7\textsuperscript{*}</td>
<td>87 ± 7\textsuperscript{*}</td>
<td>88 ± 6\textsuperscript{*}</td>
<td>85 ± 6\textsuperscript{*}</td>
</tr>
<tr>
<td>TPVR, dyn·s·cm\textsuperscript{-5}</td>
<td>1,434 ± 264</td>
<td>1,188 ± 242\textsuperscript{*}</td>
<td>1,213 ± 272\textsuperscript{*}</td>
<td>1,192 ± 228\textsuperscript{*}</td>
<td>1,174 ± 111\textsuperscript{*}</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; SV, stroke volume; CO, cardiac output; TPVR, total peripheral vascular resistance. Hemodynamic data are from the follicular phase of the menstrual cycle and at 6, 8, 10, and 12 wk of pregnancy. \textsuperscript{*}Significant difference compared with value at follicular phase.

![Graph](http://ajpheart.physiology.org/)

Fig. 1. Percent change, relative to the follicular phase (FP). In CO, filled bars and resting energy expenditure (REE, open bars). Data are presented as means and SE and originate from the FP of the menstrual cycle and at 6, 8, 10, and 12 wk of pregnancy. \textsuperscript{*}Significant difference compared with that at FP.

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Received 26 April 1999; accepted in final form 17 November 1999.
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