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

M. E. A. SPAANDERMAN, M. MEERTENS, M. VAN BUSSEL, T. H. A. EKHART, AND L. L. H. PEETERS
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Spaanderman, 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.

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; R&L 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 (V\(\dot{O}_2\), l/min) and carbon dioxide production (V\(\dot{CO}_2\), l/min; see Ref. 23). From these values, the respiratory quotient (RQ) was calculated according to the formula

\[
RQ = \frac{V\dot{CO}_2}{V\dot{O}_2}
\]

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

\[
\text{REE (kcal/24 h)} = (3.9 + 1.1RQ) \times V\dot{O}_2 \times 1,440
\]

\[
\text{REE}_{FFM} \text{ (kcal·24 h}^{-1} \cdot \text{kg}^{-1}) = (3.9 + 1.1RQ) \times V\dot{O}_2 \times 1,440/\text{FFM}
\]

where \(\text{REE}_{FFM}\) 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 semilateral 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

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

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 at the outlet 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

\[
\text{TPVR (dyn·s·cm}^{-2}) = 80 \times \text{MAP/CO}
\]

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

### 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, \(\text{REE}_{FFM}\), 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 \(\text{REE}_{FFM}\) 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 \(\text{REE}_{FFM}\) 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

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

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>29 ± 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, cm</td>
<td>168 ± 7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Parity, % nulliparous</td>
<td>50</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>91 ± 12</td>
</tr>
</tbody>
</table>

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

| Table 2. Metabolic data |
|---|---|---|---|---|
| | 6 Wk | 8 Wk | 10 Wk | 12 Wk |
| Weight, g | 65 ± 10 | 65 ± 10 | 65 ± 11 | 65 ± 11 | 65 ± 12 |
| FFM, kg | 45 ± 5 | 46 ± 4 | 44 ± 5 | 45 ± 5 | 45 ± 5 |
| REE, kcal/24 h | 1,496 ± 165 | 1,536 ± 141 | 1,451 ± 215 | 1,486 ± 201 | 1,426 ± 117 |
| \(\text{REE}_{FFM}\), kcal·24 h}^{-1} \cdot \text{kg}^{-1} | 33.5 ± 3.4 | 33.2 ± 2.9 | 31.5 ± 4.0 | 32.8 ± 3.4 | 32.8 ± 1.5 |
| RQ, l/min | 0.88 ± 0.04 | 0.88 ± 0.06 | 0.87 ± 0.04 | 0.92 ± 0.06 | 0.89 ± 0.04 |

Values are means ± SD. REE, resting energy expenditure (kcal/24 h); FFM = fat-free mass (kg), RQ, respiratory quotient. Metabolic data and body and FFM are from the follicular phase of the menstrual cycle and at 6, 8, 10, and 12 wk of pregnancy.
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 CO per unit REE and REEffM 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 an effect that has been observed by others a fall in basal metabolic rate in early 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 systemic vasorelaxation developing independently of changes in basal metabolism. How this initial change in pregnancy is induced remains to be established. Prolonged changes in steroid environment giving rise to an altered balance between vasoconstrictive and vasodilatory stimuli are thought to be responsible for the initial arterial relaxation (15, 17). The support for this concept comes from observations during the menstrual cycle and in the (pseudo)pregnant rat. During the luteal phase of the menstrual cycle, the hemodynamics and renal function change slightly in the direction similar to that observed in early pregnancy (8). In rat pseudopregnancy, initial adaptations in hemodynamic and volume homeostasis are similar to those observed in normal rat pregnancy (1, 3, 24). Moreover, although not found by all investigators, suppletion of sex steroid hormones in ovarietomized 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.

Obviously, these results should be interpreted in the context of the methods employed, particularly with respect to potential pitfalls. We performed the CO measurement immediately after the REE determination, a choice made for logistic reasons. These observations can only be considered "simultaneously made" if the participants were really in a steady state. The latter was highly probable, since REE is a continuously measured variable that can only be determined reliable when RQ had been stable for at least 15 min. The steady-state conditions during the REE measurement were maintained during the subsequent CO measurement, a condition verified on the basis of maintained steady state in HR and MAP values throughout the latter period until completion of data acquisition. These findings indicate that the early pregnancy systemic vasorelaxation develops independently of changes in basal metabolism. How this initial change in pregnancy is induced remains to be established. Prolonged changes in steroid environment giving rise to an altered balance between vasoconstrictive and vasodilatory stimuli are thought to be responsible for the initial arterial relaxation (15, 17). The support for this concept comes from observations during the menstrual cycle and in the (pseudo)pregnant rat. During the luteal phase of the menstrual cycle, the hemodynamics and renal function change slightly in the direction similar to that observed in early pregnancy (8). In rat pseudopregnancy, initial adaptations in hemodynamic and volume homeostasis are similar to those observed in normal rat pregnancy (1, 3, 24). Moreover, although not found by all investigators, suppletion of sex steroid hormones in ovarietomized 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.

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*</td>
<td>70±6*</td>
<td>67±8</td>
<td>71±7*</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*</td>
<td>5.9±1.0*</td>
<td>5.8±0.8*</td>
<td>6.1±0.4*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92±11</td>
<td>87±7*</td>
<td>87±7*</td>
<td>88±6*</td>
<td>85±6*</td>
</tr>
<tr>
<td>TPVR, dyn·s·cm⁻⁵</td>
<td>1,434±284</td>
<td>1,188±242*</td>
<td>1,213±272*</td>
<td>1,192±228*</td>
<td>1,174±111*</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. *Significant difference compared with value at follicular phase.

Fig. 1. Percent change, relative to the follicular phase (FP), in cardiac output (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. *Significant difference compared with the value at FP.

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