Different changes in resistance index between uterine artery and uterine radial artery during early pregnancy

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BACKGROUND: Changes in blood flow impedance of the uterine artery (UA) and uterine radial artery (RA) which is in the lower-extremity of the UA were examined during early pregnancy. METHODS: Blood flow impedance was assessed by transvaginal color-pulsed-Doppler-ultrasonography in 72 women from weeks 4–16 of pregnancy and expressed as a resistance index (RI). RESULTS: RA-RI remained at the late-luteal phase level until the 5th week of pregnancy, decreased until the 7th week, and remained low until the 10th week. UA-RI remained at the late-luteal phase level until the 10th week, and then gradually decreased until the 16th week. In nine women with spontaneous abortion, five out of six women with impaired growth of the gestational sac showed high RA-RI at the 6th week of pregnancy, whereas all three women with loss of fetal heart beat at the 8th week showed normal changes in RA-RI. CONCLUSIONS: Our results show different changes in blood flow impedance between the UA and RA during early pregnancy. A significant decrease of RA-RI after the 5th week may reflect vascular remodeling in the maternal–fetal interface at placentation, whereas a significant decrease of UA-RI after the 10th week may reflect changes of the whole uterine blood flow associated with uterine growth.

Keywords: uterine blood flow; uterine artery; radial artery; early pregnancy; spontaneous abortion

Introduction

Normal trophoblast invasion to the maternal decidua and decidual blood vessels is essential for successful placentation. In particular, dramatic changes in vascular structure occur in the maternal–fetal interface at placentation. Extravillous trophoblasts invade uterine spiral arteries, modifying their endothelial lining and media, and cause to a progressive dilatation of these vessels (Kam et al., 1999). The vascular remodeling in the maternal–fetal interface may reduce local arterial resistance and thereby increase uteroplacental blood flow (Lin et al., 1995; Aardema et al., 2001; Prefumo et al., 2004a). Impairment of this process is associated with pregnancy complications including spontaneous abortion, intrauterine growth restriction and pre-eclampsia (Meegdes et al., 1988; Minguillon et al., 1989; Meekings et al., 1994; Vailhe et al., 1999; Aardema et al., 2001; Lisman et al., 2004; Prefumo et al., 2004a). In addition, increased uterine vascular resistance during the luteal phase decreases the pregnancy rate with in vitro fertilization and embryo transfer (IVF–ET) (Steer et al., 1992; Bassil et al., 1995). Uterine vascular relaxation and the increase in uterine blood flow in early pregnancy appear to be important determinants of pregnancy outcome.

Doppler ultrasound has been used for many years as a non-invasive technique to assess blood flow impedance. Although a number of studies have been reported regarding the change in uterine artery (UA) blood flow to assess uteroplacental circulation during early pregnancy, the findings given so far still seem to be controversial. Some study groups (Schulman et al., 1986; Thaler et al., 1990; Makikallio et al., 2004) reported no changes in UA blood flow until the 8–10th week of pregnancy and a rapid decrease thereafter. On the other hand, others reported a linear decrease in UA blood flow between gestational weeks 4 and 14 (Jurkovic et al., 1991; Jauniaux et al., 1992; Coppens et al., 1996; Valentin et al., 1996). Recently, much attention has been focused on the uterine radial artery (RA) that crosses the myometrium, which is the lower-extremity of UAs, because it is thought to better reflect the endometrial blood flow (Zaidi et al., 1995; Chien et al., 2002; Tamura et al., 2006). It is of interest to know whether blood flow impedance of RAs reflects vascular remodeling in the maternal–fetal interface at placentation, and whether abnormal blood flow patterns of RAs are associated with early pregnancy failure. However, the change in RA blood flow during early pregnancy is also controversial. Merce et al. (1996) reported that retrochorionic blood flow, which
reflected in RA blood flow, increased progressively between the 4th and 12th week of pregnancy. Makikallio et al. (2004) also reported that the pulsatility index of the RA decreased between the 5th and 10th week of pregnancy. On the other hand, Bernstein et al. (2002) reported that RA blood flow did not significantly change between the 4th and 12th week of pregnancy. Therefore, this study was undertaken to examine the change in blood flow impedance of the UA and the RA during early pregnancy.

Materials and Methods

Patients
This study was reviewed and approved by the IRB of Yamaguchi University Graduate School of Medicine. From April 2004 to August 2006, a total of 106 women with a history of infertility, who were interested in becoming pregnant and had normal menstrual cycles, were recruited in this study. The mean age was 31.4 ± 5.4 years (mean ± SD), with a range of 23–42 years. They were non-smokers and free from major medical illness including hypertension. Women were excluded if they had myoma, adenomyosis, congenital uterine anomaly, ovarian tumor or used oestrogens, progesterone or androgens, or had chronic use of any medication, including non-steroidal anti-inflammatory agents or anticonvulsants. They received Doppler examinations during a natural menstrual cycle.

Out of 106 women, 63 women achieved a singleton pregnancy naturally (n = 33) or by the treatments [clomifene treatment cycle (n = 2), HMG–HCG treatment cycle (n = 14), IVF–ET treatment cycle (n = 14)], and nine women experienced a first-trimester spontaneous abortion. The mean interval between the first menstrual cycle studied and the last menstrual cycle followed by pregnancy was 6 months (2–18 months). The women with IVF–ET received ovarian stimulation followed by luteal support with HCG and progesterone. After pregnancy was confirmed, the women received longitudinal serial Doppler examinations weekly or every 2 weeks between the 4th and 10th week of pregnancy, and every 2–4 weeks between the 10th and 16th week of pregnancy. The day of ovulation, which was defined as the start of the 2nd week of pregnancy, was determined by ultrasonography, measurement of urinary LH or basal body temperature records.

Ultrasonography
Blood flow impedance of the UA and the uterine RA was evaluated with the use of a computerized vaginal ultrasonography with an integrated pulsed Doppler vaginal scanner [Aloka ProSound SSD-3500SV and Aloka UST-984-5 (5.0 MHz) vaginal transducer, Aloka Co. Ltd, Tokyo, Japan]. Uterine arteries were sampled lateral to the cervix near the internal os. Since RAs are in the lower extremity of UAs and the mean of the two points of RA-RI were used for statistical analyses.

Figure 1: Changes in RI of the UA and the RA during early pregnancy
After pregnancy was confirmed, 63 pregnant women underwent serial Doppler examinations weekly or every 2 weeks between the 4th and 10th week of pregnancy, and every 2–4 weeks between the 10th and 16th week of pregnancy. The UA-RI and RA-RI at the late luteal phase of the natural cycle were also shown. The box stretches from the lower quartile (defined as the 25th percentile) to the upper quartile (defined as the 75th percentile). The median is shown as a line across the box. The lower bar represents the 10th percentile, and the upper bar represents the 90th percentile. The number of women examined is indicated in parentheses. (a) P < 0.01 versus 10th week; (b) P < 0.01 versus 13th week; (c) P < 0.01 versus 5th week; (d) P < 0.01 versus 6th week (Kruskal–Wallis test followed using the Bonferroni correction).
interface. This is because vascular remodeling by trophoblast invasion may reflect vascular remodeling in the maternal–fetal interface has been associated with pregnancy complications such as spontaneous abortion, intrauterine growth restriction and pre-eclampsia (Meegdes et al, 1989; Meekings et al, 1995; Pijnenborg, 1998). It is also reported that the blood flow from the RA nearest to the placental site would be the indicator of the histological changes taking place in the implantation site (Merce et al, 1996). However, future studies are needed to determine the relationship between the Doppler RA resistance and histological features of vascular remodeling.

Our finding that the RA-RI decreased after the 5th week of pregnancy is consistent with previous reports that blood flow impedance of the RA decreased between the 4th and 12th week of pregnancy (Merce et al, 1996) and between the 5th and 10th week of pregnancy (Makikallio et al, 2004). However, our finding is not consistent with the report by Bernstein et al (2002) that RA blood flow impedance did not significantly change between the 4th and 12th week of pregnancy. The differences among these reports including the present study may be due to the distinction between cross-sectional and longitudinal study designs.

Our finding of a significant decrease of UA-RI after the 10th week of pregnancy is consistent with previous reports of no changes in UA blood flow impedance until the 8–10th week of pregnancy and a rapid decrease thereafter (Schulman et al, 1986; Thaler et al, 1990; Makikallio et al, 2004). The decline of UA-RI may reflect the change of the whole uterine blood flow which is associated with uterine growth, because the major compartment of the uterus is the myometrium, and Doppler studies of UAs reflect the blood flow impedance of the myometrium rather than the local blood flow impedance of the endometrium (Ng et al, 2006).

The decreased RA-RI at the placental site whereas UA-RI remains constant may reflect the local development of the shunts at the placental site such as between spiral arteries and intervillus space, because a lower RI in the more distal part of the uteroplacental circulation indicates the development of such shunts (Makikallio et al, 2004). This suggests the possibility that the UA-RI was not affected because the change in RA-RI is a local event.

Early pregnancy loss is a common complication of pregnancy, but the mechanisms are poorly understood except when chromosomal abnormalities are involved (van Lijnsochten et al, 1994a,b; Genest et al, 1995; Jauniaux and Hustin, 1998; Roberts et al, 2000). Impairment of vascular remodeling in the maternal–fetal interface has been associated with pregnancy complications such as spontaneous abortion, intrauterine growth restriction and pre-eclampsia (Meegdes et al, 1988; Minguillon et al, 1989; Meekings et al, 1994; Vailhe et al, 1999; Aardema et al, 2001; Lisman et al, 2004; Prefumo et al, 2004a). Vascular remodeling and the following increase in uterine blood flow in early pregnancy appear to be important determinants of pregnancy outcome (Meekings et al, 1994; Aardema et al, 2001; Prefumo et al, 2004b). Doppler studies in the first trimester have failed to demonstrate abnormal blood flow indices in the uteroplacental circulation of pregnancies that subsequently ended in spontaneous abortion (Jauniaux et al, 2005). The present study showed cases of
spontaneous abortion, with impaired growth of the gestational sac, whose RA-RIIs remained high or failed to decrease normally between the 5th and 6th week of pregnancy. The high RA-RI between the 5th and 6th week of pregnancy may be a cause of spontaneous abortion and reflect impaired vascular remodeling caused by failure of normal trophoblastic invasion at placentation (Meegdes et al., 1988; Lismam et al., 2004; Jau- niaux and Burton, 2005). Poor trophoblastic invasion and impaired modification of uterine spiral arteries have been associated with abnormally high UA Doppler resistance indices (Prefumo et al., 2004a). It is of interest to know when the high RA-RI started in these patients. Although the RA-RI may have been high from the preceding luteal phase, high RA-RI between the 5th and 6th week of pregnancy may be a useful marker of poor pregnancy outcome.

The present study showed that the changes in blood flow impedance during early pregnancy were different between UAs and uterine RAs. The significant decrease of RA-RI after the 5th week of pregnancy may reflect vascular remodeling in the maternal–fetal interface, although the trophoblast invasion is limited to the endometrial part of spiral arteries (Carter, 1997; Pijnenborg, 1998). On the other hand, the decrease of UA-RI after the 10th week of pregnancy may reflect the change in whole uterine blood flow. This study also reported cases of spontaneous abortion, with impaired growth of the gestational sac, whose RA-RIIs remained high or failed to decrease normally between the 5th and 6th week of pregnancy. The altered change of RA-RI may give a new insight into understanding the early stages of the pathophysiology of spontaneous abortion, such as at the 5–6th week of pregnancy. However, further studies are needed with larger sample sizes.

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