Original Article

The multiple reference range of mean uterine artery pulsatility index for natural and in vitro fertilization singletons during 11–14 gestational weeks

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Background: Ultrasonography of the uterine artery (UtA) in the first and second trimesters of pregnancy can assess uterine-placental blood perfusion and guide early clinical prevention. Establishing normal ranges of the UtA pulsatility index (UtA-PI) at 11–14 weeks of pregnancy is helpful for the early identification of high-risk pregnant women and improving the prognosis. This study aimed to establish a reference range of UtA-PI based on crown-rump length (CRL) for spontaneous and in vitro fertilization (IVF) singleton pregnancy during 11–14 weeks, respectively.

Methods: A prospective study was performed at Peking Union Medical College Hospital. Healthy, low-risk women with a singleton pregnancy at 11–14 gestational weeks were consecutively recruited for this study from December 2017 to December 2020. All participants underwent routine prenatal ultrasound examination. The CRL of the fetus and the UtA-PI were measured in both uterine arteries, and average values were calculated. The LMS method was used to fit the percentile (P)5, P10, P25, P50, P75, P90, and P95 curves of the UtA-PI value of spontaneous and IVF singleton pregnancy with CRL changes, respectively.

Results: A total of 1,962 pregnant women with normal fetuses were included in this study, including 1,792 pregnancies conceived naturally and 170 IVF fetuses. The UtA-PI reference range in the spontaneous pregnancy group was consistently higher than that in the IVF group during 11–14 weeks, and showed a statistically significant difference in UtA-PI for spontaneous and IVF pregnancies ($P<0.001$). According to the LMS method, each percentile curve of UtA-PI decreased with the increase of CRL in both the natural pregnancy group and the IVF group. The P95 range of UtA-PI for pregnant women with naturally conceived and IVF pregnancy was 2.74 to 2.11 and 2.50 to 1.94, respectively. The overall change of UtA-PI differentials of the two groups showed a downward trend and decreased slightly with the increase of CRL.

Conclusions: This study provided a single-center, large sample of data and constructed a CRL-based reference value of UtA-PI for spontaneous and IVF singleton pregnancy, which provides a reliable basis for early UtA evaluation and early clinical decision-making during 11–14 gestational weeks.

Keywords: Uterine artery pulsatility index (UtA-PI); crown-rump length (CRL); LMS method; percentile values

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Introduction

Prenatal uterine artery (UtA) Doppler ultrasonography is the most effective non-invasive method to directly assess uterine-placental blood perfusion. Abnormal pulsatility index (PI) in the uterine arteries is closely related to adverse outcomes for pregnant women and fetuses (1,2). UtA abnormalities can effectively predict pre-eclampsia, fetal growth restriction (FGR), placental abruption, and intrauterine death, and can be used as an auxiliary monitoring method for pregnant women and fetuses at high risk (3). In recent years, several studies have applied UtA Doppler at 11–14 weeks of gestation. Doppler ultrasonography of the UtA in the first and second trimesters of pregnancy can guide the early clinical preventive use of low-dose aspirin, which helps to improve the prognosis and reduce treatment costs (4,5). The accurate assessment of the UtA at 11–14 weeks has important clinical significance.

Establishing normal ranges of the UtA-PI is necessary to identify abnormal blood perfusion to the placenta. Most previous studies have focused on the reference of uterine arteries during middle and late pregnancy, and the normal range of UtA-PI was accepted based on the gestational week changes (6-8). At present, there are few studies on the normal range of UtA-PI during 11–14 weeks, and the interval grouping range of gestational week is relatively large. It would be helpful to construct the UtA-PI range through the crown-rump length (CRL) directly. The inaccurate gestational week or the estimation error will be avoided, which is more convenient for clinical application.

In recent years, with the development of assisted reproductive technology (ART), the number of pregnancies achieved through in vitro fertilization (IVF) has increased. However, IVF has been reported as a risk factor for maternal and fetal complications, and the placenta is thought to play an important role in the pathogenesis of the disease (9,10). Compared with spontaneous pregnancies, IVF-associated pregnancies present with different clinical scenarios or risks (11). Therefore, the different evaluation criteria for IVF should be considered. The UtA-PI is a valuable method to evaluate the impedance flow for uterine arteries. The reference range of UtA-PI for IVF fetuses at 11–14 weeks is still not well established. An accurate reference range is helpful in selecting high-risk women for this subgroup of patients.

This study aimed to analyze the characteristics of UtA-PI for singleton pregnancy during 11–14 weeks and establish the reference range of UtA-PI based on CRL for spontaneous and IVF singleton pregnancy. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-629/rc).

Methods

This prospective study was approved by the local institutional ethics review board (No. HS-953) and informed consent was provided by all participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Participants

The consecutive healthy, low-risk women with a singleton pregnancy attending for routine antenatal care or transferred from other hospitals to Peking Union Medical College Hospital at 11–14 gestational weeks were enrolled from December 2017 to December 2020. All women underwent at least one ultrasound scan in each trimester of pregnancy and underwent serial ultrasound scans during the first, second, and third trimesters.

The inclusion criteria were as follows: (I) healthy woman with an ongoing first-trimester pregnancy, no use of tobacco, recreational drugs, or excessive alcohol (defined as >50 mL/week) since becoming pregnant, and adequate nutritional status; (II) viable, singleton, CRL length of 45–84 mm; (III) normal fetal growth (>10^{th} and <90^{th}) centile on growth curves according to international standards (12,13); and (IV) spontaneous and IVF pregnancies. The exclusion criteria were as follows: (I) participants with pre-existing complications or comorbidities that may affect the measurement value of UtA [including pre-pregnancy

diabetes, immune disease (e.g., antiphospholipid antibody syndrome, systemic lupus erythematosus), cardiovascular disease, renal or liver diseases, malignancy, gynecological disease, endocrine disease, hypertension (requiring medical treatment before pregnancy), or history of preeclampsia (PE) or preterm birth in any previous pregnancy]; (II) uterine malformation or previous history with potential surgical damage of uterine arteries such as a myomectomy (lateral or bulky myometrial nodules); (III) adverse pregnancy outcome ended up with FGR, PE, eclampsia; and (IV) fetuses with chromosomal abnormalities, major fetal defects, and spontaneous abortions.

This study applied the standard formula for sampling variance of a centile of normal distribution to estimate the standard error of the percentile (P)th centile, according to the equation:

$$SE_p = SD\sqrt{\frac{1}{n}+\frac{Z_p^2}{2n}} \quad [1]$$

where SE_p corresponds to standard error; SD corresponds to standard deviation of the measurement; Z_p corresponds to the centile and standard normal distribution; n corresponds to sample size.

The precision achieved at the 5th or 95th centile in SD will reach a $SE = 0.13 \times SD$ for a sample size of 150 observations.

The UtA-PI values were analyzed in this study, including spontaneous and IVF pregnancies. All IVF pregnancies were carried out by autologous oocytes from fresh cycles (autologous-fresh IVF) or frozen cycles (autologous-frozen IVF) with or without the use of intracytoplasmic sperm injection (ICSI). The controlled ovarian stimulation (COS) and operation procedures were based on the standard protocol (14,15).

Measurement of UtA

The UtA images of all pregnant women were obtained through the ultrasound equipment GE Voluson E8, C1–5 probe (GE Healthcare Technologies, Milwaukee, WI, USA). All sonographers were accredited for fetal screening by the National Health Commission and received strict standardized training for UtA-PI measurement. A transabdominal ultrasound examination was carried out for the measurement of fetal CRL, diagnosis of any major fetal defects, and measurement of UtA-PI for all participants. According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Guidelines (16), the probe was moved laterally to the left and right after obtaining a sagittal image of the cervix. The UtA was identified and measured by color Doppler imaging where the proximal end of the UtA passed through the external iliac artery. The pulsed Doppler gate was placed over the whole width of the vessel. The angle between the sound velocity line and the UtA should be less than 30°, and the maximum systolic blood flow velocity was at least 60 cm/s; if the UtA branched out before passing through the external iliac artery, the blood flow of the branch artery was measured. At least three continuous waveforms were obtained, and the UtA spectrum PI, peak systolic velocity (PSV), and end-diastolic velocity (EDV) were acquired through automatic measurement. Each side of the UtA was measured twice, and the average of the four PI values was calculated. The measurement of CRL follows the guidelines of the Fetal Medicine Foundation (FMF). The measurement of CRL was carried out on the median sagittal section when the fetus was in a natural flexion state. The top of the head, the sacrococcyx, and the full length of the spine sagittal plane were displayed. The fetal body image was enlarged to 2/3–3/4 of the screen, and the cursor was placed on the outer edge of the skin on the top of the head to the sacrococcygeal skin (17). For each case, the CRL was measured twice and the average was calculated. The measuring unit of CRL was mm, and the average value was recorded after two measurements.

Clinical and pregnancy outcome collection

The follow-up results were obtained by mainly consulting the case or telephone follow-up records from December 2019 to December 2022. The baseline characteristics (age, medical history, pregnancy history, gravidity, parity), ultrasound examination results (CRL, UtA-PI), and pregnancy outcome [birth weight, gestational week at delivery, delivery mode, newborn transferred to intensive care unit (ICU)] were recorded.

Model constructing for UtA-PI

In this study, centile curves for UtA-PI percentage were constructed for spontaneous and IVF singleton pregnancy separately using Cole's LMS method. The LMS method fitted by penalized likelihood provides a convenient "black box" for the fitting of smooth reference centile curves. It also highlights features of the underlying distribution as the covariate changes and provides an objective tool to determine their relative importance (18). The LMS method

summarizes the changing distribution by three curves representing the median (M), coefficient of variation (S), and skewness (L), the latter expressed as a Box-Cox power. The median, coefficient of variation, and skewness as quantities were plotted as smooth curves changing smoothly with CRL. Using penalized likelihood, the three curves can be fitted as cubic splines by non-linear regression, and the extent of smoothing required can be expressed in terms of smoothing parameters or equivalent degrees of freedom (edf) (18). The model is fitted by selecting the CRL scale and edf for L, M, and S in the model, through various measures of deviance to find a model that minimizes the measure. Centile curves are smoothed curves calculated from the L curve, M curve, and S curve using the formula below:

$$\begin{cases} C_{100\alpha}(t) = M(t)\left(1 + L(t)S(t)Z_{\alpha}\right)^{1/L(t)} \\ L(t) \neq 0 \end{cases} \quad [2]$$

where Z_{α} is the normal equivalent deviation for the tail area; $C_{100\alpha}$ is the corresponding value on the 100th percentile curve at CRL; t is used to represent the value of CRL in the Eq. [2]. A total of seven centile curves were calculated from the 5th to the 95th. The 95th centile was defined as the upper limit of the abnormal UtA-PI.

Statistical analysis

Normally distributed continuous data were expressed in the form of mean ± standard deviation (SD), and abnormally distributed data were expressed as median (P25, P75). Categorical variables were expressed as numbers and percentages (%). The difference between the two evaluations was compared using Student's *t*-test or Wilcoxon test for continuous data and the chi-squared test for categorical data. The LMS Chartmaker Light (version 1.25; Medical Research Council, London, UK) was used to fit the UtA-PI reference curve, and the percentile values of UtA-PI (P5, P10, P25, P50, P75, P90, and P95) were depicted. A P value <0.05 was considered statistically significant. All statistical analyses for data were performed using the software SPSS 22.0 (IBM, Armonk, NY, USA).

Results

Baseline characteristics of pregnant women

A total of 2,348 pregnant women who had a singleton with a CRL during 11–14 weeks at normal fetal growth (>10th and <90th) centile on growth curves were selected in this study. Among them, 255 pregnant women with prenatal diabetes, hypertension, immune disease, or kidney disease who received aspirin or heparin treatment during pregnancy, 8 cases with uterine malformations or a previous history of potential surgical damage of uterine arteries, and 123 cases who ended up with FGR, PE, fetal anomalies, and spontaneous abortions, were excluded. A total of 1,962 pregnant women with normal fetuses were finally included in this study, including 1,792 pregnancies conceived naturally and 170 IVF-conceived fetuses. Among 170 women with singleton pregnancies obtained by invasive IVF/ICSI techniques, 97 were the result of autologous frozen blastocyst transfer, and 73 had autologous fresh embryo IVF pregnancy. The flowchart of this study is shown in *Figure 1*.

The average ages of pregnant women were 32 [interquartile range (IQR), 29–35] and 36 (IQR, 33–38) years in spontaneous and IVF pregnancies, respectively. Women who had become pregnant via IVF were older than women with spontaneous pregnancies (P<0.001) and had a higher proportion of primipara pregnancies [1,097/1,792 (61.2%) *vs.* 129/170 (75.9%), P<0.001]. The difference in maternal age between the two groups was significant. The mean CRLs of the two groups were 61.8±6.2 and 61.7±6.2 mm (P=0.560). The median value of UtA-PI of IVF pregnancy was lower than that of natural pregnancy [1.7 (IQR, 1.5–2.0) *vs.* 1.6 (IQR, 1.3–1.8)] and there was a significant statistical difference between them (P<0.001). For birth weight at delivery (P=0.147) and the gestational week at delivery (P=0.243), there was no statistically significant difference between the two groups. Women who conceived via IVF had a higher rate of cesarean section (52.4% *vs.* 31.0%, P<0.001). The baseline characteristics and pregnancy outcomes of these women are shown in *Table 1*.

Establishment of the reference range of UtA-PI of the UtA in spontaneous singleton pregnancy

The UtA-PI curves of P5, P10, P25, P50, P75, P90, and P95 for natural conception singleton pregnancy are shown in *Figure 2*, and the specific values are shown in *Table 2*. Each percentile curve of UtA-PI decreased with the increase of CRL. P95 was selected as the abnormal threshold of UtA-PI, and the higher limit value was 2.74–2.11 at 11–14 weeks.

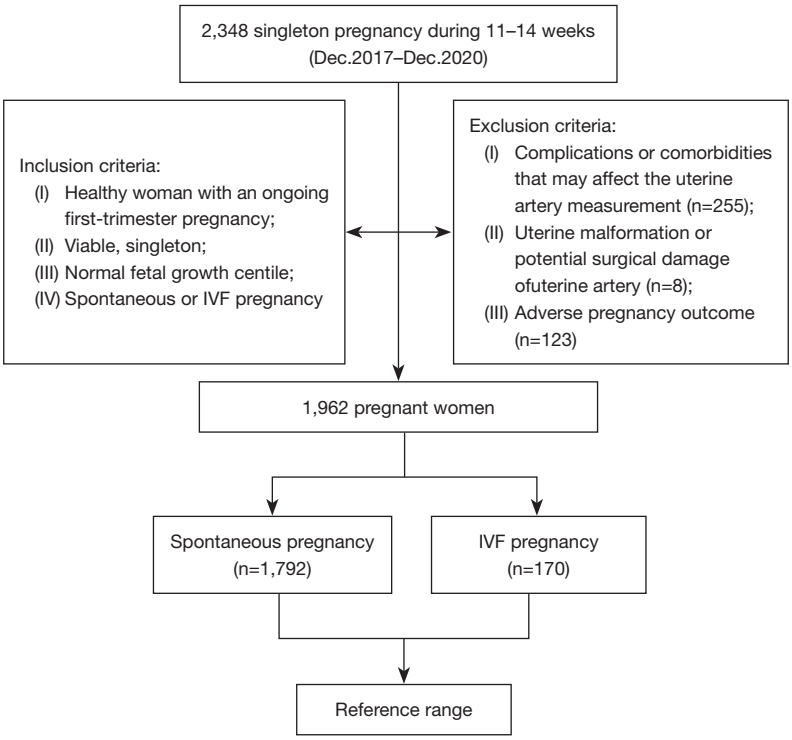

Figure 1 The flowchart of this study. IVF, in vitro fertilization.

Table 1 The baseline characteristics of 1,962 pregnant women

Characteristics	Spontaneous pregnancy (n=1,792)	IVF pregnancy (n=170)	P value
Age (years)	32 [29, 35]	36 [33, 38]	<0.001
Primipara	1,097 (61.2)	129 (75.9)	<0.001
Gravidity	2 [1, 2]	2 [1, 3]	0.050
Parity	0 [0, 1]	0 [0, 0]	<0.001
CRL (mm)	61.8±6.2	61.7±6.2	0.560
UtA-PI	1.7 [1.5, 2.0]	1.6 [1.3, 1.8]	<0.001
Pregnancy outcome			
Birth weight at delivery (g)	3,310 [3,063, 3,570]	3,360 [3,090, 3,683]	0.147
Gestational week at delivery (weeks)	39.3 [38.6, 40.1]	38.6 [39.3, 40.1]	0.243
Caesarean section	556 (31.0)	89 (52.4)	<0.001
Newborn Transferred to ICU	117 (6.5)	7 (4.1)	0.047

Data are presented as median [IQR], n (%), or mean ± SD. IVF, in vitro fertilization; CRL crown-rump length; UtA-PI, uterine artery pulsatility index; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

Establishment of UtA-PI reference range of UtA in IVF singleton pregnancy

The curves of P5, P10, P25, P50, P75, P90, and P95 of IVF singleton UtA-PI are shown in *Figure 3*, and the specific values are shown in *Table 3*. The percentile curve of the UtA-PI decreased with CRL. P95 was selected as

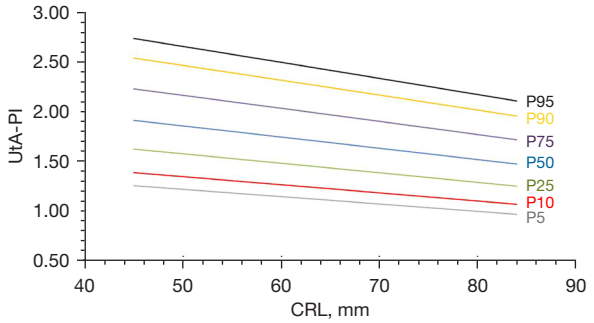

Figure 2 Percentile (5th, 10th, 25th, 50th, 75th, 90th, 95th) curves of UtA-PI for spontaneous pregnancy during 11–14 gestational weeks. UtA-PI, uterine artery pulsatility index; CRL, crown-rump length; P, percentile.

the abnormal threshold of UtA-PI, and the limit value was 2.50–1.94 at 11–14 weeks.

Comparison of the reference between spontaneous and IVF pregnancy

The P5, P50, and P95 centile curves of the spontaneous and IVF pregnancy groups are shown in *Figure 4A*. The UtA-PI reference range in the spontaneous pregnancy group was consistently higher than that in the IVF group during 11–14 weeks. The difference value of UtA-PI between the two groups at the same CRL was analyzed and is shown in *Figure 4B*. The overall change of UtA-PI differentials of

Table 2 The percentile values of UtA-PI for spontaneous pregnancy during 11–14 weeks of gestation

CRL (mm)	P5	P10	P25	P50	P75	P90	P95
45	1.25	1.39	1.62	1.91	2.23	2.54	2.74
46	1.25	1.38	1.61	1.90	2.22	2.52	2.72
47	1.24	1.37	1.60	1.89	2.20	2.51	2.70
48	1.23	1.36	1.59	1.88	2.19	2.49	2.69
49	1.22	1.35	1.58	1.87	2.18	2.48	2.67
50	1.22	1.34	1.57	1.86	2.16	2.46	2.66
51	1.21	1.34	1.57	1.84	2.15	2.45	2.64
52	1.20	1.33	1.56	1.83	2.14	2.43	2.62
53	1.20	1.32	1.55	1.82	2.12	2.42	2.61
54	1.19	1.31	1.54	1.81	2.11	2.41	2.59
55	1.18	1.30	1.53	1.80	2.10	2.39	2.58
56	1.17	1.30	1.52	1.79	2.09	2.38	2.56
57	1.17	1.29	1.51	1.78	2.07	2.36	2.54
58	1.16	1.28	1.50	1.77	2.06	2.35	2.53
59	1.15	1.27	1.49	1.75	2.05	2.33	2.51
60	1.14	1.26	1.48	1.74	2.03	2.32	2.50
61	1.14	1.26	1.47	1.73	2.02	2.30	2.48
62	1.13	1.25	1.46	1.72	2.01	2.29	2.46
63	1.12	1.24	1.45	1.71	1.99	2.27	2.45
64	1.11	1.23	1.44	1.70	1.98	2.26	2.43
65	1.11	1.22	1.43	1.69	1.97	2.24	2.42
66	1.10	1.21	1.42	1.68	1.95	2.23	2.40
67	1.09	1.21	1.41	1.66	1.94	2.21	2.38

Table 2 *(continued)*

Table 2 *(continued)*

CRL (mm)	P5	P10	P25	P50	P75	P90	P95
68	1.08	1.20	1.40	1.65	1.93	2.20	2.37
69	1.08	1.19	1.39	1.64	1.91	2.18	2.35
70	1.07	1.18	1.38	1.63	1.90	2.17	2.33
71	1.06	1.17	1.37	1.62	1.89	2.15	2.32
72	1.05	1.17	1.36	1.61	1.88	2.14	2.30
73	1.05	1.16	1.36	1.60	1.86	2.12	2.29
74	1.04	1.15	1.35	1.59	1.85	2.11	2.27
75	1.03	1.14	1.34	1.57	1.84	2.09	2.25
76	1.03	1.13	1.33	1.56	1.82	2.08	2.24
77	1.02	1.12	1.32	1.55	1.81	2.06	2.22
78	1.01	1.12	1.31	1.54	1.80	2.05	2.20
79	1.00	1.11	1.30	1.53	1.78	2.03	2.19
80	1.00	1.10	1.29	1.52	1.77	2.02	2.17
81	0.99	1.09	1.28	1.51	1.76	2.00	2.16
82	0.98	1.08	1.27	1.49	1.74	1.99	2.14
83	0.97	1.07	1.26	1.48	1.73	1.97	2.12
84	0.97	1.07	1.25	1.47	1.72	1.95	2.11

UtA-PI, uterine artery pulsatility index; CRL, crown-rump length; P, percentile.

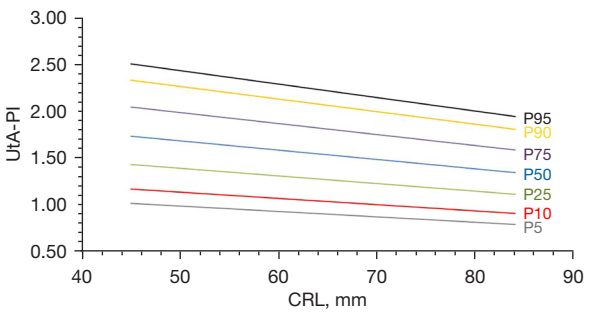

Figure 3 Percentile (5th, 10th, 25th, 50th, 75th, 90th, 95th) curves of UtA-PI for IVF pregnancy during 11–14 gestational weeks. UtA-PI, uterine artery pulsatility index; CRL, crown-rump length; P, percentile; IVF, in vitro fertilization.

the two groups showed a downward trend and decreased slightly with the increase of CRL. As the gestational age increased, the gap in UtA-PI between the two groups narrowed.

Discussion

Measurement of the UtA-PI is helpful for identifying high-risk pregnancies and screening adverse perinatal outcomes (2-4,19). This study constructed the range of transabdominal UtA-PI for each 1 mm interval in CRL based on a relatively large sample of the Chinese population during 11–14 gestational weeks. The normal ranges of UtA-PI for spontaneous and IVF singleton pregnancy were established respectively, which is more applicable for patients with different clinical conditions.

A recently published study constructed the reference ranges for UtA-PI from the first to third trimester by taking gestational age as the independent variable (20). This study used CRL as the unit to establish a more detailed PI range for the transabdominal ultrasound. The corresponding PI value can be calculated directly through CRL, which avoids the calculation error of CRL conversion to gestational weeks. In addition, the preventive use of low-dose aspirin at 11–14 weeks of pregnancy can reduce the prevalence of

Table 3 The percentile values of UtA-PI for IVF pregnancy during 11–14 weeks of gestation

CRL (mm)	P5	P10	P25	P50	P75	P90	P95
45	1.01	1.16	1.43	1.73	2.04	2.33	2.50
46	1.00	1.15	1.42	1.72	2.03	2.31	2.49
47	1.00	1.15	1.41	1.71	2.02	2.30	2.47
48	0.99	1.14	1.40	1.70	2.00	2.28	2.46
49	0.98	1.13	1.39	1.69	1.99	2.27	2.44
50	0.98	1.13	1.38	1.68	1.98	2.26	2.43
51	0.97	1.12	1.37	1.67	1.97	2.25	2.42
52	0.97	1.11	1.37	1.66	1.96	2.23	2.40
53	0.96	1.11	1.36	1.65	1.94	2.22	2.39
54	0.95	1.10	1.35	1.64	1.93	2.21	2.37
55	0.95	1.09	1.34	1.63	1.92	2.19	2.36
56	0.94	1.09	1.33	1.62	1.91	2.18	2.34
57	0.94	1.08	1.33	1.61	1.90	2.17	2.33
58	0.93	1.07	1.32	1.60	1.89	2.15	2.31
59	0.93	1.07	1.31	1.59	1.87	2.14	2.30
60	0.92	1.06	1.30	1.58	1.86	2.13	2.29
61	0.91	1.05	1.29	1.57	1.85	2.11	2.27
62	0.91	1.05	1.28	1.56	1.84	2.10	2.26
63	0.90	1.04	1.28	1.55	1.83	2.08	2.24
64	0.90	1.03	1.27	1.54	1.82	2.07	2.23
65	0.89	1.03	1.26	1.53	1.80	2.06	2.21
66	0.88	1.02	1.25	1.52	1.79	2.04	2.20
67	0.88	1.01	1.24	1.51	1.78	2.03	2.18
68	0.87	1.01	1.23	1.50	1.77	2.02	2.17
69	0.87	1.00	1.23	1.49	1.76	2.00	2.15
70	0.86	0.99	1.22	1.48	1.74	1.99	2.14
71	0.86	0.99	1.21	1.47	1.73	1.98	2.13
72	0.85	0.98	1.20	1.46	1.72	1.96	2.11
73	0.84	0.97	1.19	1.45	1.71	1.95	2.10
74	0.84	0.97	1.19	1.44	1.70	1.94	2.08
75	0.83	0.96	1.18	1.43	1.69	1.92	2.07
76	0.83	0.95	1.17	1.42	1.67	1.91	2.05
77	0.82	0.95	1.16	1.41	1.66	1.90	2.04
78	0.82	0.94	1.16	1.40	1.65	1.88	2.02
79	0.81	0.93	1.15	1.39	1.64	1.87	2.01
80	0.81	0.93	1.14	1.38	1.63	1.85	1.99
81	0.80	0.92	1.13	1.37	1.61	1.84	1.98
82	0.79	0.91	1.12	1.36	1.60	1.83	1.96
83	0.79	0.91	1.11	1.35	1.59	1.81	1.95
84	0.78	0.90	1.11	1.34	1.58	1.80	1.94

UtA-PI, uterine artery pulsatility index; IVF, in vitro fertilization; CRL, crown-rump length; P, percentile.

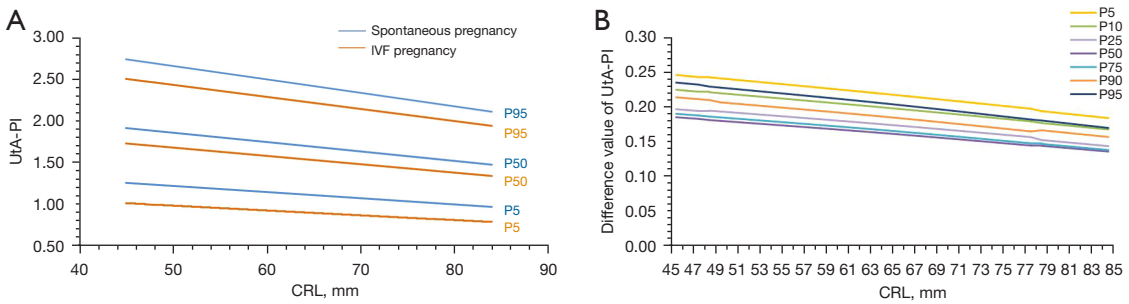

Figure 4 Comparison of different centiles of UtA-PI values for spontaneous and IVF pregnancy groups. (A) P5, P50, and P95 centile curves of UtA-PI for spontaneous (blue line) and IVF (red line) pregnancy. (B) The difference value for UtA-PI in different centile curves between the two groups at the same CRL. UtA-PI, uterine artery pulsatility index; CRL crown-rump length; P, percentile; IVF, in vitro fertilization.

placenta-related pregnancy complications and increase cost-efficiency (3,21,22). This study mainly focused on the UtA reference range of 11–14 weeks, which has important value for the early identification of high-risk pregnant women and early clinical decision-making.

There are viable methods for constructing age-related reference ranges and percentile charts. In our study, we chose the LMS method to construct CRL-related reference ranges and percentile charts. The LMS method based on empirical percentiles estimates can further analyze the underlying structure of the data and faithfully represents the data through the L, M, and S curves (19). According to a recently published study, which conducted the reference ranges for UtA-PI produced by fractional polynomial modeling from the first to the third trimester (20), the 95th centile of UtA-PI was 3.12–2.44 during the 11th to 14th gestational weeks, which is similar to the 2.74–2.11 in our study. Both the LMS method and fractional polynomial modeling can provide reliable and high-quality reference standards for UtA routine screening.

ARTs are associated with an increased risk of fetal complications. Previous studies have explored the value of UtA Doppler for this group of women (23-26). Carbone *et al.* analyzed the relationship between the method of conception and the UtA-PI and found that compared with naturally conceived fetuses, IVF can reduce log10 UtA-PI of –0.014 (–0.027, –0.002, P<0.05) through univariate regression analysis (24). Prefumo *et al.* compared the average UtA-PI of 31 IVF pregnancy cases and 62 natural pregnancy cases during 11–14 weeks (25) and reported the UtA-PI values of the two groups were 1.40 and 1.47, respectively, and there was no significant difference between the two groups (P=0.58). This study found that the UtA-PI of IVF fetuses was lower than that of naturally conceived fetuses with a statistical difference, which aligned with the results of some previous studies. It is speculated that the low UtA-PI value of IVF pregnancy may be related to the use of hormone drugs or may be related to the small sample size of IVF-conceived fetuses included in this study. In addition, a previous study also explored the difference of UtA-PI measurements in IVF/ICSI pregnancies with oocyte donation (OD) and natural conception (26). IVF/ICSI OD pregnancies demonstrated reduced UtA-PI by an average of 40% from the first to the third trimester, as compared to pregnancies that had been achieved naturally; the difference was higher at 11 weeks and reduced by about 20% at 34 weeks (26). Adjusting the specific ranges for UtA-PI reference of IVF/ICSI OD or natural conceptions may help for the greater diagnostic value of poor prognosis.

This study had some limitations. First, the differences between the two groups were an important limitation of the study. Several baseline characteristics, especially advanced maternal age, would have influenced the final results. Second, due to the gestational age being the main factor affecting UtA-PI, and the limitations of the LMS method, CRL only was used as a single variable to establish the UtA-PI reference ranges in the natural conception and IVF groups. Third, the sample size of IVF pregnancies was relatively smaller. IVF is an extremely heterogeneous procedure involving different candidates, protocols (short, long, agonist, antagonist, natural, etc.), transfer time, and medical treatment (12,15). Only women with frozen-thawed and fresh transfers were included in this study. Finally, some participant-related factors, such as any use of fertility-enhancing drugs or procedures, chronic stress, mental health, and lifestyle, were not clear, which could impact pregnancy outcomes and might influence UtA-PI.

Conclusions

This study explored the relationship between the mean UtA-PI and CRL through transabdominal ultrasound during 11–14 gestational weeks and established the reference ranges of the UtA-PI for spontaneous pregnancy and IVF pregnancy. The UtA-PI curves obtained are relatively smooth and provide a scientific basis and reference for predicting poor prognosis through the blood perfusion of the UtA.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-629/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-629/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the local institutional ethics review board (No. HS-953) and informed consent was provided by all participants.

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