

THE STUDY OF THE FETO-PLACENTAL CIRCULATION OF INTRAUTERINE GROWTH RETARDATION

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Summary

The Doppler ultrasound technique is a non-invasive, safe and easy method of studying the fetoplacental circulation. There are, however, some doubts as to the accuracy of the volumetric blood flow estimates in utero. An analysis of flow velocity waveforms, therefore, is the most useful at present in studying the fetoplacental circulation.

In intrauterine growth retardation (IUGR) cases with toxemia of pregnancy, especially those associated with proteinuria and hypertension, the fetoplacental circulation was disturbed before 20 weeks, and after 20 weeks it became markedly worse. It was thought that Doppler ultrasound technique might permit an early diagnosis of compromised fetoplacental circulation, even several weeks to months before fetal growth retardation was clinically presumed.

Introduction

Fetal survival depends on the fetoplacental circulation. Inadequate intrauterine support of the fetus due to decreased fetoplacental circulation can lead to fetal growth retardation and hypoxia. Reduced fetoplacental circulation is associated with a high risk of perinatal mortality and morbidity. Studying fetoplacental circulatory kinetics is, therefore, important in perinatal care. In 1884, the first attempts were made to study the circulation of blood in the cord of a fetal lamb¹⁾. Indeed, until relatively recently, virtually all

knowledge about fetal circulation has been based on animal studies. Much of the human data have been obtained immediately following deliveries or during abortions by hysterectomy²⁾⁻⁴⁾. Most recently, Doppler ultrasound has been widely used for non-invasive assessments of the arterial circulation. In 1980, a study of the umbilical circulation of a human fetus in utero was carried out⁵⁾⁻⁹⁾. The purpose of this study was to examine the umbilical circulatory kinetics in IUGR.

Method

The fetal body weight was estimated using the following equations;

$$1) Y=448.31X - 1679.08 \text{ (APTD} + \text{TTD}/2 < 10)$$

$$2) Y=659.69X - 3643.85 \text{ (APTD} + \text{TTD}/2 \geq 10)$$

The Japanese Fetal Growth Curve was used to diagnose IUGR. The toxemia of pregnancy was diagnosed by following criteria (Table 1).

The location of the umbilical cord and the fetal descending aorta were determined using real time B-mode ultrasound examinations. A sampling position was chosen which minimized interference from the fetal breathing movement. The fetal breathing movement interferes with the flow velocity signals in the fetal descending aorta, umbilical vein, and inferior vena cava when determining fetal blood flow¹⁰⁾. The ultrasound examinations were carried out when Doppler sound and its waveforms were stable. The diameter of the vessel and the angle between the Doppler beam and the vessel were recorded. The ultrasound system used in this study was the Toshiba

Table 1 Diagnostic criterias in toxemia of pregnancy

	Mild case	Severe case
E	Edema localized at lower extremities and increased over 500g/w of the weight	Edema appeared in the whole body
P	Proteinuria $\geq 0.3\%$	Proteinuria $\geq 2.0\%$
H	Systolic pressure $\geq 140\text{mmHg}$	$\geq 160\text{mmHg}$
	Diastolic pressure $\geq 90\text{mmHg}$	$\geq 110\text{mmHg}$

Severe case was defined as the case of filling one or more severe criterias.

E: Edema, P: Proteinuria, H: Hypertension

SAL50A-SDL01 scanning system. In this system, the real time B-mode transducer and the pulsed Doppler transducer of 2.5 MHz were combined. The FFT (Fast Fourier Transformation) was used to analyse the Doppler signals.

Subjects

Pulsed Doppler ultrasound was used to study the fetoplacental circulation in 146 pregnant

women in which 110 cases of normal course of pregnancy, 9 cases of IUGR with toxemia, and 10 cases of IUGR without toxemia were analysed. Clinical features of IUGR were shown in Table 2. This study does not include cases with maternal anemia, Rh-immunization and acute maternal bleeding, because these cases seem to be associated with increased umbilical vein flow⁷.

Principles

The measurement of blood velocity using ultrasound is based on the Doppler effect which implies that the frequency of a sound wave transmitted from a stationary source and reflected from a moving interface changes according to the velocity and direction of moving interface. The change of the frequency, called the Doppler shift, is directly proportional to the velocity of the moving interface. The Doppler shift (F) can be determined using the following equation;

$$F = \frac{2 \times f \times V \times \cos \theta}{C}$$

Table 2 Clinical features of IUGR cases

No.	Age	G&P	Gest. weeks	Fetal weight	Sex	Ap. score	Mode of delivery	Placental weight	Type of toxemia	Type of IUGR
1	30	0	39	2530	Male	9	C/S	540	PH	asymmetric
2	27	0	34	1324	Female	8	NSD	345	Pe	asymmetric
3	27	0	31	1420	Female	9	C/S	320	PHe	asymmetric
4	27	0	36	2160	Male	9	NSD	400	P	asymmetric
5	35	0	37	1710	Male	7	C/S	375	PHE	asymmetric
6	27	0	38	2080	Male	9	NSD	330	PHe	symmetric
7	25	0	38	2040	Male	9	NSD	480	P	symmetric
8	19	0	38	2570	Female	9	NSD	490	Pe	symmetric
9	37	0	38	2460	Female	9	C/S	460	PH	asymmetric
*			*		*	*	*	*	*	*
10	24	0	39	2120	Female	9	NSD	450		symmetric
11	28	0	36	1570	Male	9	C/S	360		asymmetric
12	26	0	37	2260	Male	0	NSD	495		asymmetric
13	26	0	39	2070	Male	9	NSD	415		asymmetric
14	23	0	39	2400	Female	8	NSD	430		asymmetric
15	25	0	38	2170	Female	9	NSD	370		symmetric
16	28	1	38	2460	Male	9	NSD	525		symmetric
17	33	0	38	2240	Female	10	NSD	420		asymmetric
18	26	0	40	2160	Female	9	NSD	550		symmetric
19	29	1	39	1950	Male	10	NSD	450		symmetric

Cesarian Section (C/S) was carried out in 5 cases. Four cases associated with toxemia of pregnancy. In 6 cases out of 9 cases, asymmetric IUGR were observed.

Normal spontaneous delivery (NSD) was carried out in 9 cases out of 10 cases without toxemia of pregnancy. In 5 cases out of 10 cases, asymmetric IUGR were observed.

where V is the velocity of the reflector, f is the frequency of the transmitted sound, C is the velocity of the ultrasound in the medium and θ is the angle between the emitted sound wave and the direction of moving reflector.

Using the Doppler effect, the measurement of the mean blood velocity across a vessel area is possible. Mean blood velocity was calculated using the following equation;

$$V = \frac{F \times C}{2 \times f \times \cos \theta}$$

where F is the mean frequency, f is the reference frequency, θ is the angle between the Doppler beam and the vessel, and C is the ultrasound velocity *in vivo* (1530 m/s). With two-dimensional echo ultrasound, the vessel can be easily discerned, and necessary information such as the angle between the Doppler beam and the vessel, as well as the vessel diameter can be calculated. Thus it is possible to estimate blood flow in deeplying vessels (e.g. fetal vessels in utero) using a combination of Doppler and echo ultrasound.

The volumetric blood flow (VF) in a vessel was calculated using a following equation;

$$VF = 60 \times S \times V$$

where S is the sectional area of the vessel.

The Pourcelot Ratio (PR) or the resistance index (RI) expresses the shape of the waveform in numerical form and can be used to compare peripheral resistances. PR can be calculated using the following equation¹¹⁾;

$$PR = (A - B) / A$$

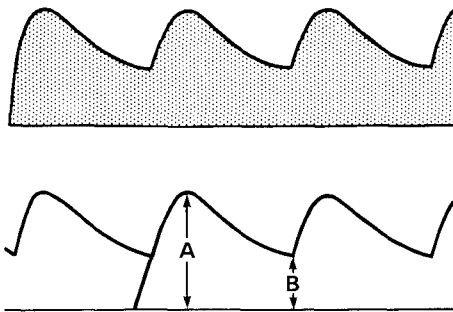


Fig. 1 The definitive schema of Pourcelot Ratio (PR)
A: peak velocity, B: end-diastolic velocity.

Results

Normal pregnancy

The inner diameter of the fetal descending aorta increased with gestational age from a mean value of 2.7 ± 0.64 cm at 17~20 weeks, to 7.16 ± 0.67 cm at 37~40 weeks. In the umbilical cord, arterial diameter increased from 2.45 ± 0.65 cm at 17~20 weeks to 4.05 ± 0.67 cm at 37~40 weeks, and venous diameter increased from 4.18 ± 0.57 cm at 17~20 weeks to 8.05 ± 0.74 cm at 37~40 weeks respectively (Fig. 2).

Mean blood velocities in the umbilical vein and artery, and in the fetal descending aorta were constant irrespective of gestational age. The mean velocity in the umbilical vein was 10.4 ± 1.78 cm/s (Fig. 3). In the umbilical artery, it was 16.70 ± 7.35 cm/s. And the mean blood velocity in the fetal descending aorta was 16.0 ± 8.96 cm/s.

The mean volumetric blood flow in the fetal descending aorta increased from 151.7 ± 54.9 ml/min at 25~28 weeks, to 321.8 ± 86.2 ml/min at 41~42 weeks (Fig. 4).

The mean volumetric blood flow in the umbilical vein increased from 149.0 ± 41.9 ml/min at

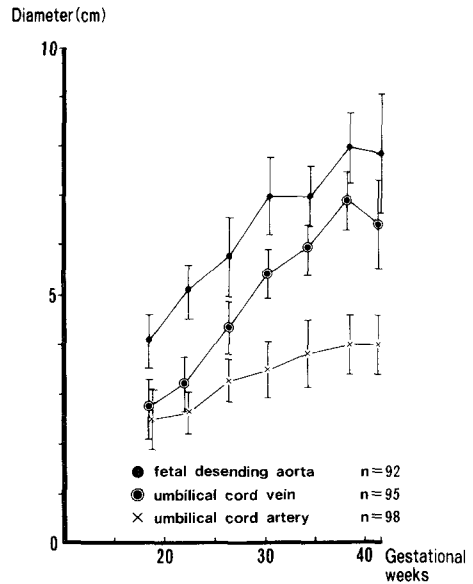


Fig. 2 Changes of inner diameter of umbilical vessels and fetal descending aorta irrespective of gestational age in normal cases

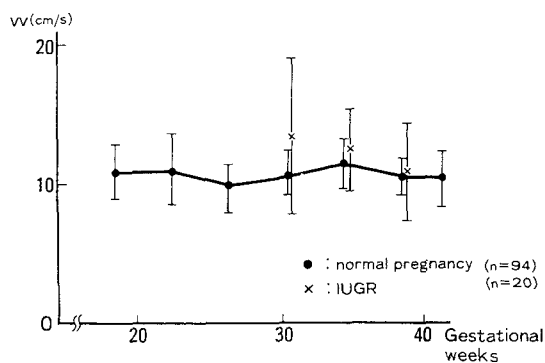


Fig. 3 The relationship between the mean blood flow velocity of umbilical vein (VV) and gestational weeks

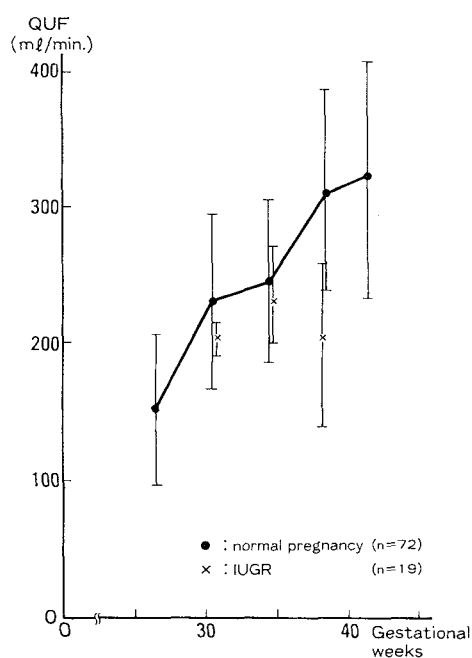


Fig. 4 The relationship between the mean volumetric blood flow in the fetal descending aorta (QUF) and gestational weeks

25~28 weeks to 314.3 ± 68.5 ml/min at 37~40 weeks. It decreased, however, to 283.1 ± 55.9 ml/min at 41~42 weeks (Fig. 5).

The mean volumetric blood flow per unit of fetal body weight in the descending aorta was constant until 32 weeks with a mean value of 124.5 ± 29.1 ml/min/kg, however, it tend to decreased gradually after 33 weeks (Fig. 6).

The mean volumetric blood flow per unit of fetal

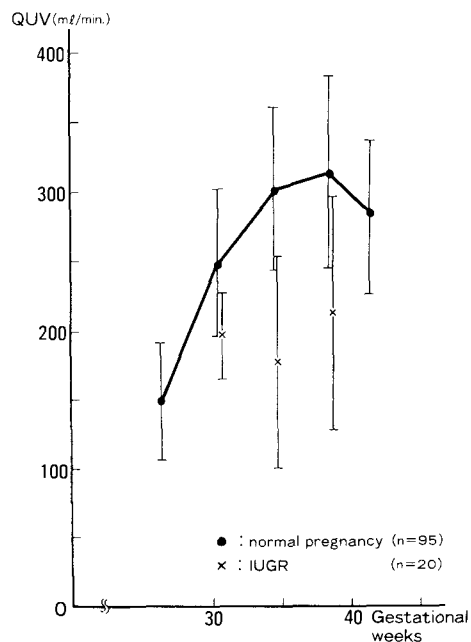


Fig. 5 The relationship between the mean volumetric blood flow in the umbilical vein (QUV) and gestational weeks

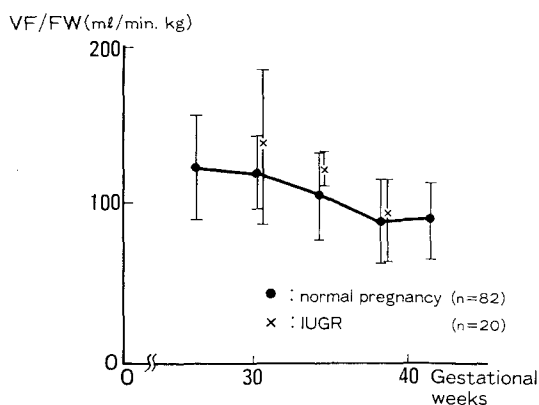


Fig. 6 The relationship between the mean volumetric blood flow per unit of fetal body weight in the fetal descending aorta (VF/FW) and gestational weeks

body weight in the umbilical vein was constant with a mean value of 130.0 ± 35.0 ml/min/kg until to 36 weeks. Beyond 37 weeks it decreased gradually with a mean value of 97.3 ± 22.3 ml/min/kg (Fig. 7).

The mean PR of the umbilical artery tended to decreased markedly from 0.75 ± 0.02 at 21~24

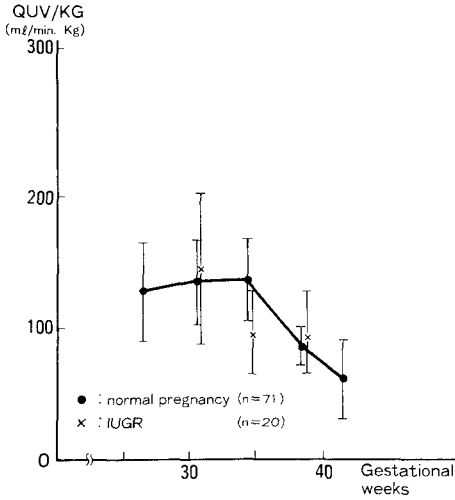


Fig. 7 The relationship between the mean volumetric blood flow per unit of fetal body weight in the umbilical vein (QUV/KG) and gestational weeks

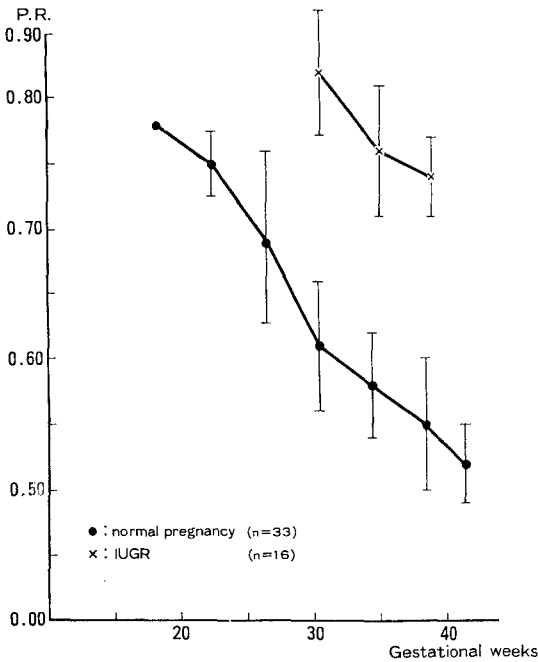


Fig. 8 The relationship between P.R. and gestational weeks

weeks to 0.55 ± 0.05 at 37~40 weeks (Fig. 8).

Sonagrams of the umbilical artery waveform showed that in normal pregnancies, downstreams became gentle slopes as gestational weeks ad-

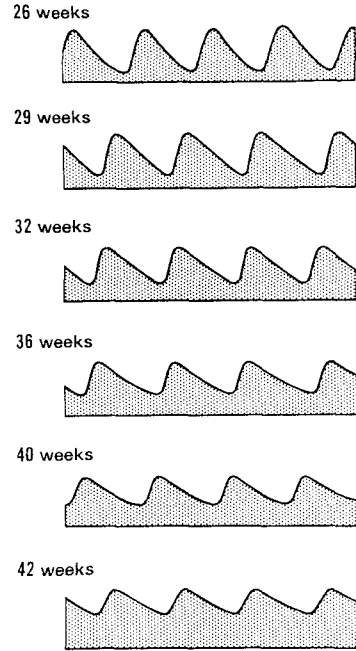


Fig. 9 Typical sonagrams of the umbilical artery waveform in normal pregnancies at various weeks

vanced (Fig. 9).

IUGR cases

The mean volumetric blood flow in the umbilical vein did not increase with a gestational age. The mean values were 197.5 ± 31.5 ml/min at 29~32 weeks, 176.5 ± 81.7 ml/min at 33~36 weeks, and 217.5 ± 83.8 ml/min at 37~40 weeks (See Fig. 5).

The mean volumetric blood flow per unit of fetal body weight in the umbilical vein decreased from 144.0 ± 57.7 ml/min/kg at 29~32 weeks to 96.0 ± 32.0 ml/min/kg after 33 weeks (See Fig. 7). In the umbilical artery, the mean blood velocity stayed constant at 15.5 ± 5.9 cm/s. The PR of the umbilical artery in IUGR cases tended to decrease keeping a high levels with a gestational age. Mean values of PR were 0.82 ± 0.05 at 29~32 weeks, 0.76 ± 0.05 at 33~36 weeks, and 0.74 ± 0.03 at 37~40 weeks (See Fig. 8).

Comparison of the fetoplacental blood flow between normal cases and IUGR cases

At about 30 weeks of gestation, the volumetric blood flow of the umbilical vein in IUGR cases was significantly lower than in normal cases with a

Table 3 Comparison of umbilical venous flow (QUV) and Pourcelot Ratio (PR) between normal cases and IUGR cases at 30 weeks of gestation

	QUV			PR		
	N	Mean	SD	N	Mean	SD
Normal cases	19	249.5	54.7	7	0.69	0.08
IUGR cases	4	197.5	36.4	4	0.82	0.06
Significant difference(p)	<0.10			<0.05		

Table 4 Comparison of umbilical venous flow (QUV) and Pourcelot Ratio (PR) between normal cases and IUGR cases at 34 weeks of gestation

	QUV			PR		
	N	Mean	SD	N	Mean	SD
Normal cases	10	303.6	60.4	3	0.56	0.03
IUGR cases	4	176.5	94.3	3	0.76	0.06
Significant difference(p)	<0.05			<0.01		

Table 5 Comparison of fetoplacental flow parameters between normal cases and IUGR cases at term

	N	VA(cm/s)	N	PR	N	QV(ml/m)	N	QF(ml/m)
Normal fetuses	20	17.1±8.3	9	0.55±0.06	20	314.3±70.2	19	308.8±78.5
IUGR fetuses	6	13.3±1.8	10	0.74±0.03	12	220.0±93.8	12	206.5±64.3
Significant difference(p)		<0.10		<0.01		<0.05		<0.01

VA : flow velocity of umbilical artery, PR : Pourcelot Ratio, QV : the volumetric flow of the umbilical vein, QF : the volumetric blood flow in the fetal descending aorta.

mean value of 197.5 ± 36.4 ml/min. And PR was significantly higher in IUGR cases than in normal cases with a mean value of 0.82 ± 0.06 . At about 34 weeks, same results were obtained with a mean value of 176.5 ± 94.3 ml/min, and 0.76 ± 0.06 (Mean \pm SD) (Table 3, 4).

During the term, the mean volumetric blood flow of the umbilical vein and the blood flow velocity of the umbilical artery were significantly low in IUGR cases. The PR was significantly higher in IUGR cases than in normal cases (Table 5).

Comparison of the fetoplacental blood flow between IUGR with toxemia of pregnancy and IUGR without toxemia of pregnancy

Table 6 Comparison of PR and the blood flow velocity of the umbilical artery (VA) in preterm

	N	PR	Blood velocity (cm/sec.)
IUGR cases with toxemia	6	0.81 ± 0.05	11.8 ± 4.4
IUGR cases without toxemia	1	0.71	21.0
Significant difference		*****	*****

In IUGR cases with toxemia of pregnancy, PR and the blood velocity of the umbilical artery were significantly higher than in IUGR cases without toxemia of pregnancy (Table 6, 7). We obtained two types of waveforms in IUGR cases, one was seen in IUGR cases with toxemia of pregnancy where downstream was either decreased or absent. The other in IUGR cases without toxemia where diastolic flow was decreased or absent and a steep upstream was present (Fig. 10).

And we obtained two regression curves of PR in this study (Fig. 11). One is in the IUGR cases without toxemia of pregnancy (C), the other in the IUGR cases with toxemia of pregnancy (A).

Table 7 Comparison of PR and the blood flow velocity of the umbilical artery in term

	N	PR	Blood velocity (cm/sec.)
IUGR cases with toxemia	3	0.77 ± 0.02	9.33 ± 0.47
IUGR cases without toxemia	6	0.72 ± 0.02	13.71 ± 4.9
Significant difference (p)		<0.05	<0.05

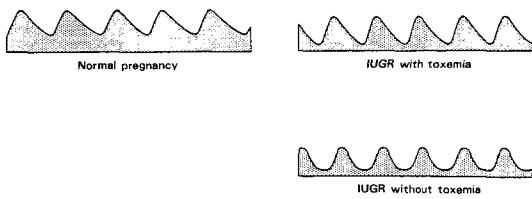


Fig. 10 Sonograms obtained in this study of umbilical artery waveform in IUGR cases

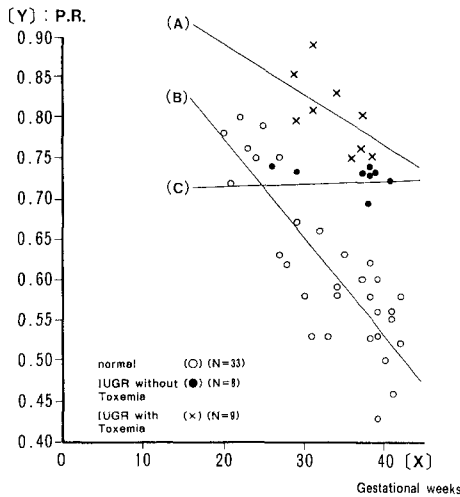


Fig. 11 Sample regression curves of PR
 A: IUGR cases with toxemia, $Y = -0.0073X + 1.045$, $R = +0.460$, $N=8$, B: normal cases, $Y = -0.021X + 1.02$, $R = -0.85$, $N=33$, C: IUGR cases without toxemia, $Y = -0.002X + 0.7224$, $R = -0.013$, $N=7$.

Discussion

Many investigators have studied fetoplacental circulation using Doppler ultrasound technique. Gill⁵ reported that in normal fetuses, umbilical venous blood flow increased with gestational age until 36 weeks, hit a maximum between 37 and 38 weeks, then decreased during the last 2 weeks of pregnancy. Their findings showed that the volumetric flow per unit of fetal body weight was constant with a mean value of 120 ml/min/kg up until 36 to 37 weeks, when a reduction occurred. Eik-Ness and associates⁶ have reported an average flow of 110 ml/min/kg in patients at term. Jouppila et al⁷ obtained a value of 101 ml/min/kg. Kurjak et al⁸ obtained a value of 107 ml/min/kg. More recently, Griffin et al⁹ have recorded an

average flow of 122 ml/min/kg during the third trimester in normal fetuses. In this study, the umbilical venous volumetric blood flow of normal fetuses increased with a gestational age until 37 weeks, hit a maximum at 38 weeks, then decreased during the last 2 weeks. The flow per unit of fetal body weight was constant with a mean value of 130 ml/min/kg up until 35 to 36 weeks, when reduction occurred. Although Gill⁵ reported a reduction of umbilical flow below the normal range in 6 out of ten, third trimester IUGR cases, the findings of this study did not show a significant difference in flow per unit of fetal body weight between IUGR and normal fetuses in spite of a reduction of umbilical venous blood volumetric flow in IUGR cases.

Recently, with the increased use of Doppler ultrasound for studying fetoplacental circulation, new problems in measuring blood volumetric flow *in vivo* have appeared¹²⁻¹⁴. 1) Determining the diameter of the vessel; For the fetus in the later stages of pregnancy, the vessel diameters range between 6 and 8 mm, and therefore, an error of only 0.4 mm will cause an error of 10% in the resulting flow. It is worth noting that for a 4 mm vessel, an error of 0.4 mm changes the flow measurement by 25%. In this study, umbilical venous diameters were always greater than 4 mm from 20 weeks, and fetal aortic diameter reached to 4 mm at 24 weeks. However umbilical atrial diameters stayed less than 4 mm throughout the gestational period. 2) The angle between the Doppler beam and the vessel; An error in estimating the blood flow may result from an error in determining the angle between the Doppler beam and the vessel. The same error in the angle will cause a small error if the angle is small and a large error if the angle is large. Since in this study, applied angles were limited to less than 60 degrees in all cases, error caused by the angle might be negligible. 3) The profile of the Doppler beam; The Doppler signals must be filtered using a high-pass filter to remove signals from the slow-moving tissue in the path of the beam as well as those from the vessel wall movement. An ultrasound frequency of 2.0 MHz

and a 100 Hz high-pass filter were chosen as the most suitable for taking measurement on fetuses in utero.

At present, therefore, an analysis of the waveform would be the most useful in studying the fetoplacental circulation. The umbilical artery waveform depends primarily on the placental impedance downstream and the cardiac contractility upstream. The main indices of peripheral impedance in the umbilical artery are the A/B, Pulsatility Index and Pourcelot Ratio (or Resistance Index)¹²⁾. These indices were defined as follows;

A/B	$A/B = f_{\max}/f_{\min}$
Pulsatility Index	$PI = (f_{\max} - f_{\min})/f_{\text{mean}}$
Pourcelot Index (or Resistance Index)	$PR = (f_{\max} - f_{\min})/f_{\max}$

Coefficient variations for these indices were as follows;

A/B	0.6
PI	1.3
PR	0.6

There are some reports which have recorded placental impedance value for normal pregnancies using A/B ratio and PR. FizGerald and associates¹³⁾ reported that there was a significant reduction in PR with advancing gestational age in normal pregnancies. Stuart and associates¹⁴⁾ reported that A/B ratio declined progressively with advancing gestational age, indicating a progressive reduction in placental resistance.

In this study, similar results were obtained. The umbilical artery waveform analysis has shown that in normal pregnancies, a placenta is an organ of low vascular resistance and that the placental resistance to blood flow declines with advancing gestational age. This is thought to be due to the continued growth of arterio-venous anastomosis in placental villi¹⁵⁾¹⁶⁾.

FizGerald and associates¹²⁾ reported that significant increases in RI values were observed in 77% of all IUGR cases. Griffin and associates⁹⁾ reported that IUGR cases, especially those associated with proteinuria and hypertension showed increased PI and lower diastolic velocities

than normal. In this study, there were significant difference in PR and the blood velocity of the umbilical artery between IUGR cases with toxemia and IUGR cases without toxemia at term. During the preterm, similar difference were noted. These facts indicate that in IUGR cases with toxemia of pregnancy, the fetoplacental circulation was disturbed and became markedly worse.

Sato and associates¹⁷⁾ suggested that there may be a critical point of RI at about 20 weeks, and that placental resistance declines markedly until 20 weeks of pregnancy. In accordance with this, it was thought that there might be a pathophysiological difference between IUGR cases with toxemia and IUGR cases without toxemia, especially those associated with proteinuria and hypertension, and that the low blood flow velocity and the high resistance of the umbilical artery were resulted in reduction of placental microcirculation before 20 weeks of pregnancy.

Conclusion

In normal pregnancies, there was a definite relationship between the umbilical venous flow and the gestational age. That is, the flow increased as the pregnancy advanced. The PR (Pourcelot Ratio) or RI (Resistance Index) which is an indication of the peripheral resistance of the umbilical artery, markedly decreased as pregnancy progressed. In IUGR cases with toxemia (proteinuria and hypertension) the fetoplacental circulation became worse as time progressed.

It was thought that in IUGR cases with toxemia, a disturbance of fetoplacental circulation might occur before 20 weeks of pregnancy and that Pourcelot Ratio of the umbilical artery might permit an early diagnosis of compromised the fetoplacental circulation even several weeks to month before fetal growth retardation is clinically presumed.

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子宮内胎児発育遅延 (IUGR) における胎児胎盤循環動態に関する研究

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ドップラー超音波法は胎児胎盤循環動態を研究する上で、非侵襲性の安全かつ簡便な方法である。しかし、血流量の計測上その精度にはやや問題がある。

したがって、胎児胎盤循環の評価上、流速波形の解析が現在のところ最も有効な方法である。

妊娠中毒症、特に蛋白尿と高血圧を伴う子宮内胎児発育遅延例では、胎児胎盤循環は妊娠20週以前にすでに障害されていることが推察され、妊娠20週以後は著しく悪化した。ドップラー超音波法を使用すれば、胎児の発育遅延が臨床上推定可能となるよりも数週間から数カ月前という時点で、胎児胎盤循環悪化の早期診断が可能になると考えられた。