

# Effect of ritodrine tocolysis on fetal cardiac output distribution to the placenta

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**Background:** Adequate placental perfusion is important for fetal development and well-being, but the effect of tocolysis on placental perfusion is unclear. The aim of this study was to evaluate changes in fetal cardiac output distribution to the placenta following ritodrine tocolysis. **Methods:** This retrospective study involved 244 ultrasound findings in 142 singleton cases of appropriate for gestational age fetuses. The fetal cardiac output distribution to the placenta was defined and calculated as the percentage of umbilical vein flow volume (UVFV) based on the combined cardiac output (CCO). Ultrasound findings of 28 patients in the ritodrine group and 114 patients in the control group were compared using the unpaired *t*-test and Mann-Whitney U-test. **Results:** The CCO and UVFV increased as gestation progressed. On the other hand, distribution to the placenta was constant at approximately 15% from 28 to 35 weeks of gestation. Compared with the control group, the ritodrine group showed a significant increase in fetal heart rate, and the CCO also increased. The increase in UVFV in the ritodrine group was attributed to a significant increase in both the umbilical vessel diameter and blood flow velocity. As a result, distribution to the placenta in the ritodrine group was constant at about 20% and had a 5% increase at each week of gestation compared to the control group. **Conclusions:** To conclude, ritodrine tocolysis increased the fetal cardiac output distribution to the placenta. Additional research is required to determine whether tocolysis improves the placental perfusion in fetal growth restriction due to reduced placental perfusion.

## Keywords

Distribution to the placenta; Doppler ultrasound; Fetal cardiac output; Ritodrine; Umbilical vein flow volume

## 1. Introduction

Adequate perfusion of the placenta and fetal organs is necessary for normal fetal growth and well-being. Recent developments in ultrasound technology have enabled the reproducible and accurate recording of flow volumes, providing additional important physiological information about fetal placental perfusion, including combined cardiac output (CCO) and umbilical vein flow volume (UVFV).

CCO is an indicator of myocardial function [1]; however, it is of limited value as it is load load-dependent. UVFV is closely related to the placental cotyledon mass and indicates the oxygen levels and nutrients transferred from the mother

to the fetus. Moreover, the evaluation of blood flow distribution can provide important physiological information [2]. Chronic hypoxia caused by limited placental perfusion, associated with placental dysfunction, restricts fetal growth, whereas decreased placental perfusion during slight uterine contractions reduces the oxygen supply, causing late decelerations. In these circumstances, tocolytic drugs and bed rest are often used empirically to prevent the occurrence of slight uterine contractions that may lead to fetal hypoxia [3].

Ritodrine is a beta-sympathomimetic agent used for tocolysis in several countries. Doppler analyses indicated that ritodrine induces favorable changes in placental perfusion. Ritodrine passes through the placenta, enters the fetal circulation, and increases the fetal heart rate, resulting in increased fetal cardiac output. In addition, controlling uterine contractions may improve placental blood flow by reducing placental perfusion pressure [4]. Hence, the favorable effects of ritodrine tocolysis on placental perfusion may be applied to fetal growth restriction associated with placental dysfunction. However, the effects of ritodrine on placental perfusion and the ability of the fetus to handle oxygen deficiencies remain unclear. This study aimed to evaluate changes, following ritodrine tocolysis, in fetal cardiac output distribution to the placenta.

## 2. Methods

### 2.1 Study population

This was a retrospective cross-sectional study. The study participants and the exclusion criteria are shown in Fig. 1. Given the risk of preterm labor, bed rest or ritodrine administration was started upon admission. Bed rest is advised when there is cervical length shortening; whereas, ritodrine is administered when there are evident uterine contractions. A ritodrine infusion in 5% glucose was initiated at a dose of 50  $\mu\text{g}/\text{min}$  and was increased to a maximum of 200  $\mu\text{g}/\text{min}$  until the maternal symptoms subsided. Gestational ages were determined based on the crown-rump lengths before 12 weeks of gestation or the mother's last regular menstrual period.

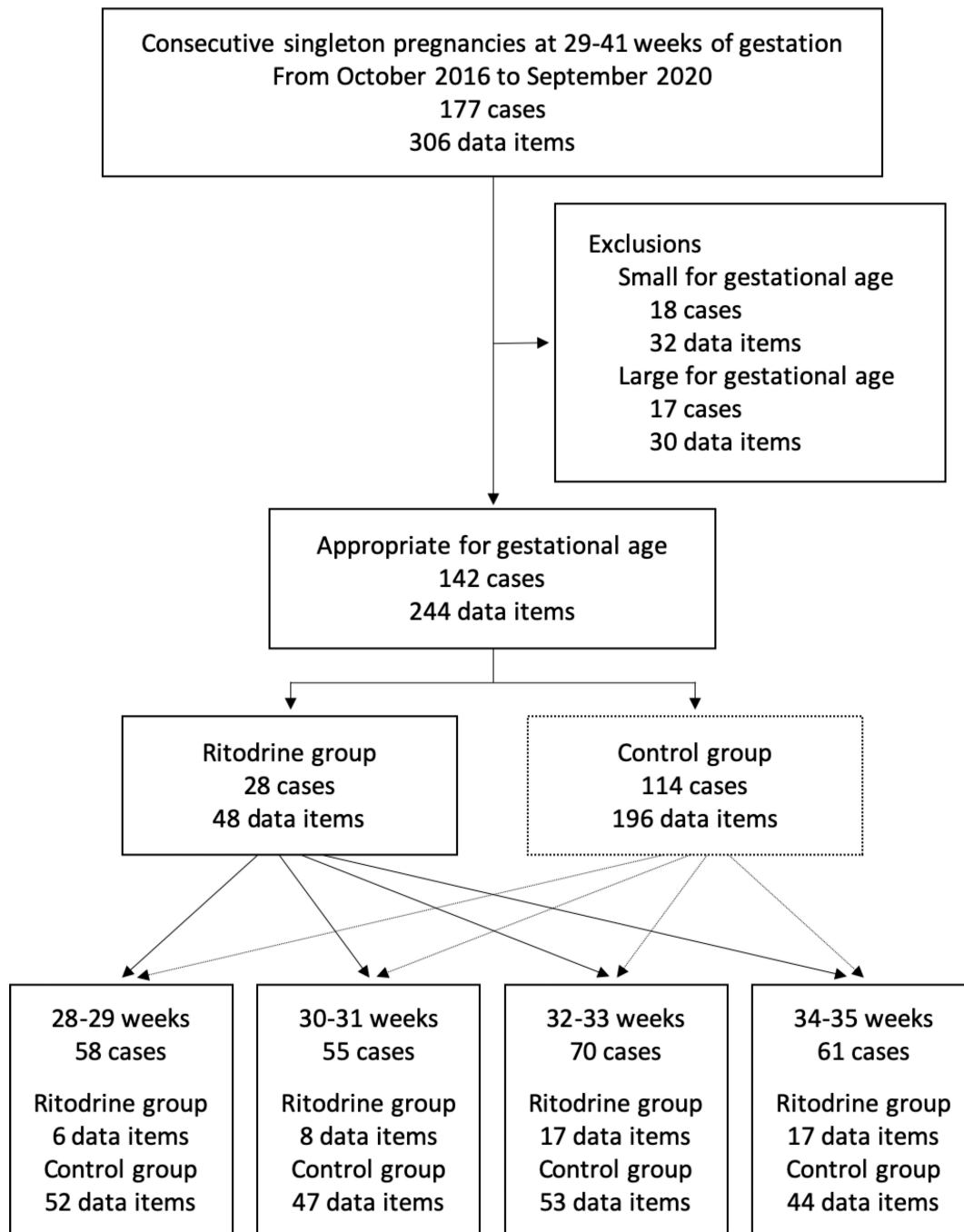


Fig. 1. Study participants and exclusion criteria.

## 2.2 Sonography

The participants' pregnancies were examined during a 30-min ultrasound session. All examinations were performed by a single sonographer using a Voluson E8 ultrasound system (GE Healthcare Japan Corporation, Tokyo, Japan) equipped with a RAB4-8-D probe (GE Healthcare Japan Corporation, Tokyo, Japan) set on low frequency.

All fetal blood vessel diameters were measured twice, and the average values were calculated. The inner diameter (D) of the aorta and the pulmonary artery was measured perpen-

dicular to the vessel wall between the open semilunar valves in the zoomed images. The sample volume was placed at the ostia of the aorta and the pulmonary artery, and the maximum velocity during systole was recorded for 2–3 s during fetal quiescence. The angle correction was kept as low as possible. The systolic time-velocity integral (TVI) and heart rate (HR) were calculated from the average of three cardiac cycles. The left and right ventricular outputs were calculated as  $\pi \cdot (D/2)^2 \cdot TVI \cdot HR$ , and CCO was calculated as the sum of the left and right ventricular outputs.

**Table 1. Background of all cases and comparison between the ritodrine group and the control group.**

	All cases (n = 142)	Ritodrine group (n = 28)	control group (n = 114)	<i>p</i>
GA at birth	37 w 5 d ± 16 d	35 w 2 d ± 17 d	38 w 2 d ± 13 d	<0.001
Birth weight (g)	2729 ± 477	2323 ± 529	2828 ± 47	<0.001
Birth weight (SD)	0.05 ± 0.76	0.11 ± 0.79	0.03 ± 0.75	0.538
Apgar score 1 min	8.0 ± 1.4	7.2 ± 1.7	8.2 ± 1.2	<0.001
Apgar score 5 min	9.1 ± 0.9	8.5 ± 1.2	9.3 ± 0.7	<0.001
Umbilical blood pH	7.294 ± 0.067	7.296 ± 0.068	7.294 ± 0.067	0.8
Weight of placenta (g)	579 ± 100	584 ± 136	578 ± 91	0.517
Male	73 (51.4%)	11 (39.3%)	62 (54.4%)	0.284
Primiparous	61 (43.0%)	13 (46.4%)	48 (42.1%)	0.677

Mean ± SD/number of cases (%).

GA, gestational age; SD, standard division.

For UVFV, the diameter of the intra-abdominal umbilical vein (D) was measured before that of the first portal branches perpendicular to the vessel wall. The time-averaged maximum velocity (TAMXV) was recorded over 5–10 s with the angle correction oriented along the axis of the vessel when fetal breathing movements were not observed. The UVFV was calculated as  $\pi \cdot (D/2)^2 \cdot TAMXV \cdot 1/2$ . The distribution to the placenta was defined and calculated as the percentage of UVFV based on the CCO. Fetal weights were estimated during ultrasound examinations [5].

### 2.3 Statistical analyses

All data were expressed as means and standard deviations. The assumption of normality was checked for each variable. Continuous variables were compared using the unpaired *t*-test or *u*-test, and categorical variables were compared using the Fisher's exact or the Chi-square test. Statistical significance was set at  $p < 0.05$ . Statistical analyses were carried out using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [6], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

A total of 306 ultrasound evaluations were performed in 177 cases with no obstetric complications other than threatened preterm delivery. We analyzed 244 data items from 142 cases, excluding small and large for gestational age neonates. This included 48 data items in 28 cases in the ritodrine group and 196 data items in 114 cases in the control group. Ultrasound findings were compared between the two groups at each week of gestation (Fig. 1).

Table 1 shows the background of all cases and a comparison between the ritodrine and the control groups. The ritodrine group had a lower gestational age at birth (35 w 2 d ± 17 d vs. 38 w 2 d ± 13 d,  $p < 0.001$ ) and a lower birth weight (2323 ± 529 g vs. 2828 ± 47 g,  $p < 0.001$ ). There was no difference in standard deviation (SD) values based on standard birth weight (0.11 ± 0.79 vs. 0.03 ± 0.75,  $p = 0.538$ ). Umbilical cord arterial blood pH (7.296 ± 0.068 vs. 7.294 ± 0.067,

$p = 0.800$ ) and weight of the placenta (584 ± 136 g vs. 578 ± 91 g,  $p = 0.517$ ) did not differ between the two groups.

Table 2 shows comparisons of ultrasound Doppler findings between the two groups at each week of gestation. The CCO was significantly higher in the ritodrine group than in the control group during the periods of 28 w 0 d to 29 w 6 d, and 34 w 0 d to 35 w 6 d. Although no significant difference was observed, it suggests that the ritodrine group tended to have a higher CCO than the control group during the periods of 30 w 0 d to 31 w 6 d, and 32 w 0 d to 33 w 6 d. When the left and right ventricular stroke volumes were examined separately, both left cardiac output (LCO) and right cardiac output (RCO) tended to be higher in the ritodrine group than in the control group, but there was no statistical significance. In each period, the increase in cardiac output was associated with a significant increase in HR, with no significant increase in the TVI. The UVFV was significantly increased in the ritodrine group compared with the control group in each period. This was associated with a significant increase in both umbilical vein vessel diameter and umbilical vein blood flow velocity. As a result, distribution to the placenta tended to be significantly higher in the ritodrine group than in the control group, and a statistically significant difference was observed after 30 weeks of gestation. The umbilical artery pulsatility index (PI) was significantly lower in the ritodrine group than in the control group after 32 weeks of gestation. There was no difference in middle cerebral artery PI between the two groups during each period.

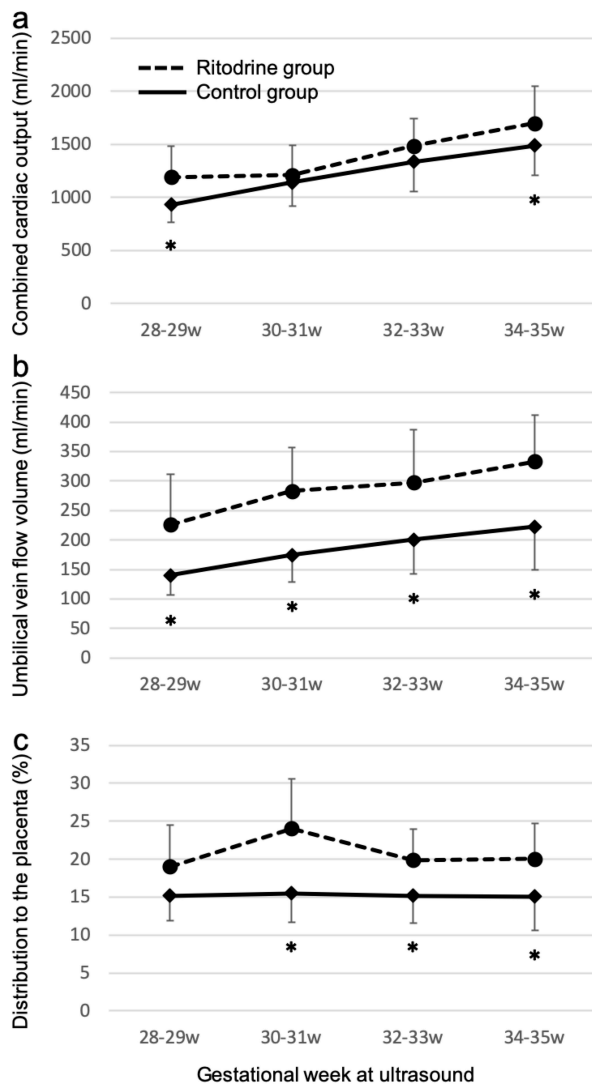
Fig. 2 shows the changes in CCO, UVFV, and distribution to the placenta according to the weeks of gestation. CCO and UVFV tended to increase as the gestational weeks increased. On the other hand, distribution to the placenta was constant at about 15% from 28 to 35 weeks of gestation. CCO and UVFV tended to increase significantly in the ritodrine group compared with the control group. As a result, distribution to the placenta significantly increased after 30 weeks of gestation.

**Table 2. Comparisons of ultrasound Doppler findings between the two groups at each weeks of gestation.**

	28 w 0 d–29 w 6 d			30 w 0 d–31 w 6 d			32 w 0 d–33 w 6 d			34 w 0 d–35 w 6 d		
	Ritodrine (n = 6)	Control (n = 52)	<i>p</i>	Ritodrine (n = 8)	Control (n = 47)	<i>p</i>	Ritodrine (n = 17)	Control (n = 53)	<i>p</i>	Ritodrine (n = 17)	Control (n = 44)	<i>p</i>
EFBW (g)	1259 ± 171	1312 ± 156	0.443	1678 ± 214	1619 ± 150	0.193	1940 ± 177	1912 ± 163	0.536	2289 ± 192	2226 ± 168	0.211
CCO (mL/min)	1190 ± 291	933 ± 165	0.024*	1209 ± 283	1140 ± 221	0.435	1484 ± 257	1337 ± 285	0.062	1700 ± 348	1490 ± 283	0.018*
LCO (mL/min)	500 ± 188	428 ± 94	0.122	525 ± 138	512 ± 115	0.77	659 ± 130	599 ± 153	0.151	759 ± 177	662 ± 120	0.016*
LOT HR (bpm)	155 ± 6	146 ± 8	0.008*	15 ± 11	142 ± 10	0.009*	152 ± 10	141 ± 9	<0.001*	151 ± 12	142 ± 8	<0.001*
mean LOT d (mm)	0.57 ± 0.06	0.56 ± 0.05	0.411	0.63 ± 0.06	0.61 ± 0.05	0.351	0.68 ± 0.04	0.67 ± 0.05	0.644	0.71 ± 0.05	0.70 ± 0.06	0.339
LOT TVI (cm/s)	12.2 ± 3.5	12.1 ± 1.5	0.878	11.2 ± 3.0	12.3 ± 2.0	0.19	12.0 ± 1.7	12.0 ± 2.4	0.891	12.4 ± 1.7	12.2 ± 1.7	0.729
RCO (mL/min)	690 ± 202	505 ± 101	0.057	685 ± 175	628 ± 132	0.291	825 ± 165	738 ± 180	0.08	941 ± 195	828 ± 208	0.059
ROT HR (bpm)	157 ± 8	145 ± 9	0.003*	153 ± 8	144 ± 11	0.028*	151 ± 6	143 ± 8	<0.001*	150 ± 13	142 ± 7	0.006*
mean ROT d (mm)	0.70 ± 0.07	0.65 ± 0.06	0.021*	0.74 ± 0.06	0.71 ± 0.06	0.161	0.80 ± 0.07	0.76 ± 0.06	0.076	0.83 ± 0.06	0.80 ± 0.07	0.136
ROT TVI (cm/s)	11.1 ± 1.6	10.6 ± 1.5	0.522	10.4 ± 1.5	11.2 ± 1.9	0.259	10.9 ± 1.7	11.3 ± 1.8	0.392	11.5 ± 1.6	11.4 ± 2.2	0.981
UVFV (mL/min)	226 ± 85	140 ± 33	<0.001*	283 ± 74	174 ± 46	<0.001*	297 ± 89	201 ± 59	<0.001*	333 ± 79	222 ± 73	<0.001*
mean UVD (mm)	0.56 ± 0.09	0.49 ± 0.05	0.012*	0.62 ± 0.09	0.55 ± 0.07	0.011*	0.63 ± 0.09	0.58 ± 0.07	0.022*	0.68 ± 0.08	0.60 ± 0.07	<0.001*
UVF (cm/s)	29.7 ± 4.0	24.5 ± 4.7	0.007*	31.5 ± 5.5	24.7 ± 4.3	<0.001*	31.5 ± 6.9	24.7 ± 4.4	<0.001*	30.1 ± 3.6	25.7 ± 5.4	<0.001*
Distribution (%)	19.0 ± 5.5	15.2 ± 3.3	0.122	24.0 ± 6.6	15.5 ± 3.8	<0.001*	19.9 ± 4.0	15.2 ± 3.6	<0.001*	20.0 ± 4.7	15.1 ± 4.5	<0.001*
UA-PI	0.98 ± 0.19	1.08 ± 0.18	0.226	0.94 ± 0.14	1.01 ± 0.19	0.377	0.84 ± 0.17	0.96 ± 0.19	0.02*	0.77 ± 0.13	0.91 ± .15	0.001*
MCA-PI	1.90 ± 0.33	1.90 ± 0.32	0.999	2.11 ± 0.22	1.93 ± 0.35	0.168	1.99 ± 0.30	1.91 ± 0.35	0.447	1.65 ± 0.38	1.76 ± 0.33	0.299

Mean ± SD.

EFBW, estimated fetal body weight; CCO, combined cardiac output; LCO, left cardiac output; LOT HR, left outflow tract heart rate; LOT d, left outflow tract diameter; LOT TVI, left outflow tract time velocity integral; RCO, right cardiac output; ROT HR, right outflow tract heart rate; ROT d, right outflow tract diameter; ROT TVI, right outflow tract time velocity integral; UVFV, umbilical vein flow volume; UVD, umbilical vein diameter; UVF, umbilical vein flow; UA-PI, umbilical artery-pulsatility index; MCA-PI, middle cerebellum artery-pulsatility index; \*, *p* < 0.05.



**Fig. 2. Comparison of the ultrasound Doppler findings at each week of gestation between the control group and the ritodrine group.** (a) Combined cardiac output. (b) Umbilical vein flow volume. (c) Distribution to the placenta. The dotted line indicates the ritodrine group, the solid line indicates the control group, and the error bar indicates the standard deviation. \* $p < 0.05$ .

Regardless of the weeks of gestation, the ritodrine group showed a significant increase in fetal HR and tended to increase cardiac output as compared with the control group. The ventricular outflow tract diameter and TVI were almost the same between the two groups. The increase in UVFV in the ritodrine group was attributed to a significant increase in both umbilical vein diameter and blood flow velocity. As a result, distribution to the placenta was constant at approximately 20% in the ritodrine group and increased by approximately 5% compared with the control group between 28 and 35 weeks of gestation.

#### 4. Discussion

Ritodrine tocolysis significantly increased CCO, UVFV, and placental distribution of fetal blood flow. Ritodrine administration also increased fetal HR, which contributed to the increase in CCO. A previous study showed that ritodrine tocolysis significantly increased fetal HR and LCO [4]. Although that study did not consider vessel diameter, ritodrine did not change the ventricular outflow tract diameter and TVI in this study.

In this study, ritodrine tocolysis increased the umbilical venous diameter and UVFV. UVFV usually increases only with increasing vessel diameter according to gestational age [7, 8]. Furthermore, fetal breathing movements increase the umbilical vein's blood flow, diameter, and blood flow velocity [9], but they do not affect fetal HR or umbilical arterial blood flow waveform. We believe that UVFV was augmented by ritodrine tocolysis. However, it remains unclear whether the vessel diameter dilation was caused by ritodrine directly or by passive dilation as a consequence of increased blood flow. We propose that the increase in UVFV resulted from a decrease in placental villous vascular resistance due to ritodrine-induced vasodilation.

Other investigators have described reductions in the Doppler indices associated with the umbilical artery, following ritodrine tocolysis [10, 11]. In this study, the uterine artery PI decreased in the ritodrine group in cases with more gestational weeks. These findings suggest that ritodrine acts as a vasodilator of the fetal vasculature. It has also been reported that ritodrine increases the extensibility and volume of large blood vessels and reduces peripheral vascular resistance [12]. We expect that lower peripheral vascular resistance in the fetus contributes to an increase in the distribution of cardiac output to the placenta.

The distribution to the placenta decreases in patients with fetal growth restriction and placental dysfunction [2]. In growth-restricted fetuses, absolute and relative UVFV are lower [13, 14], while CCO is relatively normal, which seems to augment the recirculation of the umbilical blood within the fetal body. Hence, bed rest and tocolytic drugs may be used empirically for patients with fetal growth restriction [3]. The findings of this study showed that ritodrine tocolysis increased the distribution of cardiac output to the placentas of fetuses that were developing normally. Whether ritodrine tocolysis can increase the distribution of cardiac output to the placenta in patients with fetal growth restriction and placental dysfunction remains unclear. However, if the distribution to the placenta can also be augmented in these patients, it may be possible to increase oxygen delivery to the fetal tissue. The clinical question is whether tocolytic drugs improve distribution to the placenta, which is reduced in FGR, and whether it leads to improvement in chronic hypoxia. We think it is necessary to consider these in future research. In fetal physiology, ritodrine increases cardiac output due to fetal tachycardia, but tocolytic drugs other than ritodrine may not increase cardiac output. If UVFV increases without an increase

in cardiac output, the rate of increase in distribution to the placenta will be higher. We think it is important to understand how distribution to the placenta changes with tocolytic drugs other than ritodrine.

We acknowledge that evaluation of the distribution to the placenta is not possible for all outpatients who undergo routine pregnancy check-ups using ultrasound; hence, there was a potential for selection bias. While we limited the level of error by using a single sonographer, the lack of repeatable measurements was a limitation of our study.

## 5. Conclusions

In summary, ritodrine tocolysis increases the distribution of fetal cardiac output to the placenta, which is largely attributable to a greater increase in UVFV compared to CCO. We believe that tocolytic drugs increase the distribution to the placenta and improve the low-oxygen concentrations that are present in growth-restricted fetuses.

## Abbreviations

UVFV, umbilical vein flow volume; CCO, combined cardiac output; TVI, time-velocity integral; TAMXV, time-averaged maximum velocity.

## Author contributions

RS designed the research study and analyzed the data. RS, TS, and KM performed the operation and collected the data. KM supervised the study. All authors contributed to editorial changes in the manuscript. All the authors approved the final version of the manuscript.

## Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol for this study was approved by the ethics committee of Gifu University Hospital, Gifu, Japan (approval number: 29-380). This was a retrospective study, and the data used for statistical analyses were collected from medical records. All laboratory tests were performed on patients as a routine practice. The Ethics Committee did not require written informed consent from each patient, but instead required printed information (post-out) to be provided about the study. All participants were given the opportunity to refuse inclusion of their data in the study.

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## Conflict of interest

The authors declare no conflict of interest.

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