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Effects of drugs of placental insufficiency on Doppler blood flow indices and its pregnancy outcomes analysis in the third trimester of pregnancy

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Abstract

Background: Placental insufficiency is a common and serious complication of the placenta during pregnancy, which affects about 10 to 15% of pregnancy. Placental insufficiency is one of the common clinical problems in obstetrics for mothers and fetuses because it is still a potential cause of preterm birth, preeclampsia, fetal growth restriction, and stillbirth. In the case of placental insufficiency, the placenta cannot provide enough oxygen and nutrition from the mother's blood to the fetus, which leads to fetal growth restriction, intrauterine fetal distress, low birth weight, stillbirth, neonatal asphyxia, or some birth defects later. Doppler ultrasound is a common method to evaluate the degree of placental blood circulation damage. However, until now, there is no consensus on the standard definition, specific diagnostic criteria, and common treatment guidelines for placental insufficiency.

Aim: to analyze the effects of drugs (low-molecular weight heparin in single therapy **LMWH** and fluids replacement therapy in single therapy **FRT** or in combination therapy **LMWH+FRT** on ultrasonic Doppler blood flow indices and pregnancy outcomes of placental insufficiency in the third trimester of single pregnancies.

Materials and Methods: 120 single pregnant Chinese women were included in this study from September 2019 to December 2020. 60 pregnant women with a high S/D ratio of the fetal umbilical artery in late single pregnancy were studied retrospectively as the case group, and 60 normal pregnant women with a normal S/D ratio of the fetal umbilical artery were taken as the control group in the same period. Among the cases, 22 cases were treated with low-molecular-weight heparin (LMWH), 16 were treated with maternal fluids replacement therapy (FRT), and the others 22 were treated with LMWH + FRT. After 10 days of medication, the Doppler ultrasound blood flow indices (S/D ratio of the fetal umbilical artery and PS, PI, RI of the middle cerebral artery) were observed, and the indices before and after treatment were compared to observe the effectiveness of these drugs. Meanwhile, the pregnancy outcomes of the case group (n=60) and the control group (n=60) were recorded and compared.

Results: The study found that the mean S/D ratio of fetal umbilical artery in case group and control group was respectively 3.46±0.45 and 2.18 ±0.34, P-value= 0.000, had statistical significance before treatment; and was respectively 2.57 ±0.76 and 2.29 ±0.34, P-value = 0.000 was statistically significant too after treatment, which indicates that the S/D ratio of the fetal umbilical artery has significant significance in the evaluation of placental insufficiency.

Further analysis showed that the **women treated with LMWH**, the mean value of S/D ratio of fetal umbilical artery before and after LMWH treatment was respectively 3.26± 0.84 and 2.25 ±0.25; the mean value of S/D ratio in the fetal umbilical artery before and after treatment was significantly different, which indicates that LMWH alone had a certain effect on improving fetal umbilical blood flow. For the **women treated with FRT**, the mean value of S/D ratio of fetal umbilical artery before and after treatment was respectively 3.07± 0.86 and 2.93 ±0.66; there was no significant difference in the mean value of S/D ratio between the two groups before and after treatment, FRT alone has little significance in reducing the ratio of S/D of the fetal umbilical artery, indicating that the effect of FRT alone was not good, and effective as other drugs. For the **women treated with LMWH+FRT,** the mean value of S/D ratio of fetal umbilical artery before and after treatment was respectively 3.12± 1.16 and 2.60 ±0.76; the mean value of S/D ratio in fetal umbilical artery before and after treatment was significantly different,

which indicates that LMWH + FRT was more effective than single FRT, and the effect was similar to that of LMWH alone. Furthermore, Compared with the normal control group, the mean value of fetal and maternal outcomes in the case group was low, which indicates that pregnant women in the case group are more likely to have a variety of adverse fetal and maternal outcomes, such as premature delivery, low fetal weight during delivery, small gestational week, low Apgar score during delivery; We also found that the incidence of premature delivery, cesarean section, low Apgar score (< 6), amniotic fluid abnormality, placental morphology abnormality, cord abnormality, low birth weight (< 2500g), neonatal asphyxia, stillbirth and NICU admission was higher than those in the normal control group.

Conclusion: Low-molecular-weight heparin (LMWH) alone or a combination of low-molecular-weight heparin and fluids replacement therapy (LMWH + FRT) as a potential treatment of placental insufficiency in late single pregnancies can significantly reduce the S/D ratio of the fetal umbilical artery, suggesting that, it has a significant effect on the improvement of placental function. Moreover, fetal and maternal adverse pregnancy outcomes were associated with placental insufficiency in the third trimester of single pregnancies.

Keywords: Placental insufficiency; low-molecular-weight heparin (LMWH); fluids replacement therapy (FRT); Systolic/Diastolic ratio(S/D ratio); Pregnancy outcomes.

Introduction

Placental insufficiency usually refers to the aging changes of the placenta since the second and third trimester of pregnancy, accompanied by the decline of placental function, resulting in the disorder of blood exchange between the uterus and placenta, the lack of fetal oxygen and nutrients, causing some adverse perinatal outcomes like prematurity, oligohydramnios, FGR, fetal distress, fetal hypoxemia or acidosis leading to stillbirth, neonatal asphyxia or postnatal short-term or long-term cognitive and mental deficiencies. However, this definition is still unclear and not standardized in the current medical literature.

The concept of Placental insufficiency mostly used in the medical articles to designate the reduced placental function, is inaccurately defined, and the way it is currently used in the medical literature has never been scientifically studied and globally recognized [1]. Placental insufficiency is one of the common clinical challenges in obstetrics practice, and it is becoming a great problem worldwide for both mothers and babies[2, 3]. As a severe complication, if it is not detected and managed as early as possible, it can result in dangerous health complications for both infant and mother [4]. Placental insufficiency, which can affect 10 to 15% of pregnancies seems to be a probable cause of preterm labor, FGR, preeclampsia, and stillbirth [5]. Some studies have shown that Placental insufficiency leading to FGR occurs in around 8% of all pregnancies [6, 7]. However, placental ischemic diseases (PID) such as placental insufficiency, are leading to stillbirth worldwide [8]. 3 million stillbirths detected globally each year, up to half are growth restricted mostly due to uteroplacental insufficiency [9].

The main etiologies that may cause placental insufficiency are still not clear. The recognized related maternal risk factors including preeclampsia or other maternal hypertensive disorders, diabetes, anemia, maternal smoking, maternal illegal drug use including cocaine or heroin, maternal alcohol consumption, maternal taking drugs interfering with fetal growth, maternal blood clotting disorders, placenta abruption, placenta previa, abnormal umbilical cord insertion, primiparity, advanced maternal age, and previous history of delivery of FGR babies [10]. Placental insufficiency is commonly due to the onset of abnormal placental growth and development or placental impairment, thus leading to insufficient blood flow, nutrients, and oxygen supply in the placenta to maintain the adequate aerobic growth of the fetus [11, 12]. The pathophysiology mechanisms behind this low placental function, abnormal placental development, and placental damage are unknown [3]. However, Placental insufficiency is mostly linked with some unhealthy lifestyle behaviors or basic chronic diseases of the pregnant woman resulting in spiral placental vascular blood flow disorders such as atherosis, thrombosis, inflammation, infarction of placental spiral arteries followed by perfusion defects of intervillous space by maternal blood [13-15]. Studies have revealed that trophoblast-differentiation paths such as endovascular, interstitial, and chorionic villous deficiencies and trombo-occlusive impairment of the placenta could affect the pathophysiology of early-onset placental insufficiency and FGR [16, 17].

Placental insufficiency's up-to-date diagnosis still relies on nonspecific and nonstandard clinical symptoms, signs, and laboratory findings. Nevertheless, during placental insufficiency, women who have been pregnant before may find out low fetal movement or decreased uterus growth comparing to previous pregnancies [18]. The diagnosis of placental insufficiency is made based on initial observation of clinical symptoms followed by confirmation with the following diagnostic tests**:**

- **fetal movement counting:** fetal movements less than ten movements /2hours or a reduction in fetal movements more than 50**%**[19].
- **Electronic fetal monitoring(EFM)**: also known as Non-stress test, NST) reporting less than two accelerations in 30min, each one variability above baseline less than 15bpm and lasting less than 15secondes or FHR less than 120bpm in the third trimester[20].
- **Doppler ultrasound:** monitoring the abnormalities in fetal and maternal placental blood circulation. It appears to be the most common and accurate diagnostic tool for placental insufficiency [5, 27, 28].
- **Magnetic resonance imaging (MRI):** showing placental thickness, area, volume, placenta to amniotic fluid signal intensity (SI) ratio, apparent diffusion coefficient (ADC), and size of flow voids FVs [23]. A decreased ADC as an early sign of placental damage may reveal pregnancy complications like placental insufficiency associated with FGR [24].
- **Histopathology test** (placental biopsy): showing the following microscopic clinical features: chorionic villi fibrosis, utero-placental clotting, infarction, fibrin withdrawals, or a reduction in number and surface area of the villous capillaries. It seems to be one of the most accurate diagnostic tools of placental insufficiency [5].
- **Biochemical blood tests**: often used in placental insufficiency assessment include: Alpha-fetoprotein (AFP), Human placental lactogen (HPL), unconjugated estriol3 (uE3), Estrogens, placental growth factor (PlGF), vascular endothelial growth factor(VEGF), soluble FMS-like tyrosine kinase-1(sFlt-1), human chorionic gonadotrophin (hCG), pregnancy-associated plasma protein-A (PAPP-A), placental protein 13 (PP-13), etc [25, 26].

Doppler check-up of the placental flow has increased the diagnosis of placental abnormalities. Doppler ultrasound of the umbilical artery (UA), middle cerebral artery (MCA), the uterine artery, and ductus venous (DV) is considered as indicator of perinatal outcomes of pregnancies complicated with placental insufficiency. Moreover, placental insufficiency is often associated with abnormal Doppler blood flow in UA, MCA and DV [5, 27].

The UA Doppler velocimetry has become the most significant and most assessed vessel of the fetus in the exploration of his blood flow. Doppler velocimetry of the UA can detect pregnancies with high vascular impedance on the fetal side of the placenta and then pick the women in need of adequate follow-up. It is a significant marker of placental injury [5, 28]. Among its numerous indices, the S/D ratio, the pulsatility index (PI), and the resistance index (RI), are the most frequently investigated in obstetrical practice. The umbilical arterial resistance indices, expressing the resistance in assessing fetal and placental flow are increased in the fetus with uteroplacental insufficiency due to multiple causes [29].

Doppler velocimetry of fetal MCA has a significant utility in the assessment of fetal well-being, FGR, Fetal anemia, and other adverse fetal outcomes such as asphyxia and intracranial anomalies or hemorrhage. It is a precious adjuvant method to the umbilical artery in assessing placental function. The MCA most assessed indices are MCA PI, PS, RI [30, 31].

High S/D ratio > 3 after 30weeks of pregnancy in the umbilical artery and PS>80cm/s, PI <0.7, RI <0.55 in the middle cerebral artery, and other unusual changes in UA, MCA and DV which predict the high placental resistance leading to poor placental perfusion are considered as the standard and accurate diagnosis criteria of placental insufficiency [5, 28, 29].

Furthermore, When Using Doppler ultrasound to measure the fetus size, the reduced fetal biometry (BPD<8,5cm, HC<30cm, AC< 30cm, FL< 6,5cm) at the last trimester of pregnancy is also a predictive tool in the detection of placental insufficiency related to FGR despite the challenges due to some errors [25]. The amniotic fluid volume (AFV) in the single deepest vertical pocket and the amniotic fluid index (AFI) measured by antepartum routine Doppler ultrasound are also the detection tools for Oligohydramnios (AFV≤2cm, AFI≤5 cm) which predicts the onset of placental insufficiency leading to FGR or other adverse pregnancy outcomes [32, 22, 33].

Despite no effective drugs for placental insufficiency in the common obstetrical field, some advances in the prevention and its related obstetric diseases such as FGR and preeclampsia have been established [34]. Delivery is the only practical treatment choice in managing placental insufficiency. The only challenge is that sometimes there is a requirement of prolongation of gestation to reach potential fetal maturity [35].

Besides, the supplementation of main substrates essential for fetal growth, including oxygen, glucose, amino acids, fatty acids, multivitamins, and Other factors, including insulin-like growth factors and glucocorticoids administration is also considered as a fundamental option in managing placenta insufficiency. Also, the use of antioxidant therapies, including vitamins C and E, has been presented to improve poor placentation in case of placental insufficiency [37].

Some studies have evidenced that heparin, aspirin, and maternal fluids rehydration effectively increase placental blood flow and stimulates neo-angiogenesis. Thus, they are becoming potentially effective medications for placental insufficiency [38].

1. LMWH (Low-Molecular-Weight Heparin): is mostly indicated for prophylaxis of placental vascular thrombosis and infarction in the treatment of placental insufficiency. Dalteparin (Fragmin), enoxaparin (Lovenox), and fondaparinux (Arixtra) are the common used anticoagulant drugs in obstetrical practice. Due to their long half-life, simple self-administration at home, few adverse reactions (bleeding, osteoporosis, heparin-induced thrombocytopenia, skin irritation at the injection site, elevated liver enzymes, etc.), and no regular checking-up of the blood test [39]. Only Secure administration is needed during the peripartum period to prevent post-partum hemorrhage [40]. Placental insufficiency mostly displays placental clotting and infarction, leading to unusual coagulation disorder in the placenta. And Some data show that Heparins as anticoagulant therapy impact trophoblast growth and progress by decreasing apoptosis and inflammation [41].

2. FRT (Fluids Replacement therapy): Decreased amniotic fluid is intimately related to chronic placental insufficiency. No effective treatment has been proved long term, but short term simple maternal fluids supplementation (Amino acids, Dextrose or Fructose, Ringer Lactate, Multivitamins, Normal saline, etc.) has been tested as the best intervention of increasing amniotic fluid volume (AFV) to prevent and manage the placental insufficiency related to oligohydramnios [42, 43]. And some studies have also revealed that oral maternal hydration with the isotonic solution, water and intravenous fluids infusion improves amniotic fluid index (AFI) in normal pregnancies and pregnancies complicated with oligohydramnios [44, 45].

3. LDA (Low-Dose Aspirin): as an antiplatelet drug has several functions at the placental vascular wall that may prevent FGR and its related placental abnormalities by blocking the creation of prostaglandins and thromboxanes via its permanent inactivation of the cyclooxygenase enzyme [38]. It has been indicated during pregnancy generally to prevent or postpone the early-start of preeclampsia, and other indications such as the prevention of FGR, placental insufficiency, stillbirth, preterm birth and early pregnancy loss [41]. According to some studies, it is recommended to use Aspirin at low doses of 75-100mg (81 mg/d) after 12 weeks of pregnancy until 35 weeks in women who are at high risk for preeclampsia and other indications such as placental insufficiency, FGR, unexplained recurrent miscarriage, preterm birth, early pregnancy loss and stillbirth [46]. The side effects of LDA include a low risk of vascular events, colorectal cancer, and a high risk of bleeding complications (gastrointestinal, cerebral vaginal, etc.). The balance between the benefits and risks of LDA therapy differs extensively in diverse clinical situations and causal risks [47].

The aim of this study is to analyze the effects of drugs (low-molecular-weight heparin in single therapy and fluids replacement therapy in single or combination therapy) on ultrasonic Doppler blood flow indices and pregnancy outcomes of placental insufficiency in the third trimester of single pregnancies.

Materials and Methods

Study materials and methodology: 120 single pregnant Chinese women were included in this study from September 2019 to December 2020. 60 pregnant women with a high S/D ratio of the fetal umbilical artery in late single pregnancy were studied retrospectively as the case group, and 60 normal pregnant women with a normal S/D ratio of the fetal umbilical artery were taken as the control group in the same period. Among the cases, 22 cases were treated with LMWH, 16 were

treated with FRT, and the other 22 were treated with LMWH + FRT. The treatment time was 10 days, a single course. After 10 days of medication, the Doppler ultrasound blood flow indices (S/D ratio of the fetal umbilical artery and PS, PI, RI of the middle cerebral artery) were observed. The indices before and after treatment were compared to observe the effectiveness of these drugs. Meanwhile, the pregnancy outcomes of the case group (n=60) and the control group (n=60) were recorded and compared.

Inclusion criteria

1. Single pregnancies after 28 weeks of gestation.
2. All pregnancies diagnosed with placental insufficiency basing on abnormal S/D ratio of the fetal umbilical artery.

Exclusion criteria

1. Multiple pregnancies before 28 weeks of gestation.
2. Pregnancies with placental insufficiency based on other diagnosis methods rather than Doppler ultrasound such as abnormal NST, low fetal movement, FGR indexes measure, MRI, histopathology test, and so on.
3. Patients with normal S/D ratio of the umbilical artery.

Statistical analysis: We analyzed the data by using IBM statistical package for social sciences (SPSS) version 23. Qualitative and quantitative values were compared by using the Chi-square test and One-way ANOVA (analysis of variance) statistical tests with the level of significance set at.

Results

Table 1: Demographic and clinical characteristics of study cases and control group pregnant women

Indices	Cases (n = 60)	Controls (n = 60)	P-value
Age (years)	30.88±3.97	31.50±4.53	0.429
BMI (kg/m^2)	25.48±4.70	26.37±3.32	0.237
Abnormal S/D ratio (%)	60(100)	0(0)	0.000
Abnormal FGR indexes (%)	37(61.7)	0(0)	0.000
Oligohydramnios (%)	27(45)	0(0)	0.000
HDP (%)	9(15)	2(3.3)	0.053
GDM (%)	13(21.7)	8(13.3)	0.337
ICP (%)	1(1.7)	0(0)	1.000
Embolism (%)	5(8.3)	0(0)	0.057
Placenta previa (%)	3(5)	7(11.7)	0.322
Placenta abruption (%)	1(1.7)	0(0)	1.000
Anemia (%)	8(13.3)	4(6.7)	0.362
Uterus Scar (%)	12(20)	14(23.3)	0.825
Baby Congenital malformations (%)	8(13.3)	3(5)	0.204

The mean abnormal S/D ratio for the case and control groups was respectively 60(100%)) and 0(0%), p-value=0.000 ($p \leq 0.05$) was statistically significant.

Table 2: USED DRUGS Cross tabulation

		Cases	Controls	Total
USED	**LMWH group**	22	0	22
DRUGS		36.7%	0.0%	18.3%
	FRT group	16	0	16
		26.6%	0.0%	13.4%
	LMWH+FRT group	22	0	22
		36.7%	0.0%	18.3%
	Control group	0	60	60
		0.0%	100%	50%
Total		**60**	**60**	**120**
		100.0%	100.0%	100.0%

Table 3: Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	120.000[a]	5	0.000
Likelihood Ratio	166.355	5	0.000
Linear-by-Linear Association	86.4371	1	0.000
Number of Valid Cases	120		

a. 6 cells (50.0%) have expected count less than 5.
b. The minimum expected count is 50.

We conducted cross-tabulation on drugs usage for both case and control groups. The cross-tabulation results lead to a p-value=0.000, which was statistically significant.

Table 4: Ultrasound blood flow indices before drugs use

Indices	Cases (n = 60)	Controls (n = 60)	P-value
UA S/D ratio	3.46±0.45	2.18±0.34	0.000
MCA PS	47.41±9.30	50.30±9.27	0.091
MCA PI	1.55±0.31	2.78±10.35	0.361
MCA RI	0.74±0.09	0.72±0.09	0.171

Table 5: Ultrasound blood flow indices after drugs use

Indices	Cases (n = 60)	Controls (n = 60)	P-value
UA S/D ratio	2.57±0.76	2.29±0.34	0.000
MCA PS	50.42±10.83	54.83±11.07	0.056
MCA PI	1.56±0.31	1.50±0.28	0.269
MCA RI	0.80±0.22	0.75±0.07	0.149

The mean S/D ratio of fetal umbilical artery in case group and control group was respectively 3.46±0.45 and 2.18±0.34, P-value= 0.000, had statistical significance before treatment; After treatment, the results were respectively 2.57±0.76 and 2.29±0.34, P-value=0.000 was statistically significant too. In other indexes P-value was more than 0.05, which has no statistical significance.

Table 6: Ultrasound blood flow indices changes before and after drugs use

Indices	Before or After treatment	LMWH group	FRT group	LMWH+FRT group	Control group	P- value
UA S/D ratio	Before treatment	3.26±0.84	3.07±0.86	3.12±1.16	2.18±0.34	0.000
	After treatment	2.25±0.25	2.93±0.66	2.60±0.76	2.29±0.34	0.000
MCA PS	Before treatment	39.14±6.04	48.63±8.23	46.91±11.01	50.30±9.27	0.091
	After treatment	58.72±10.97	49.78±10.05	50.56±11.97	54.83±11.07	0.056
MCA PI	Before treatment	1.44±0.29	1.49±0.32	1.71±0.27	2.78±10.35	0.361
	After treatment	1.53±0.26	1.51±0.35	1.65±0.27	1.50±0.28	0.269
MCA RI	Before treatment	0.71±0.13	0.76±0.10	0.79±0.07	0.72±0.09	0.171
	After treatment	0.76±0.06	0.78±0.23	0.84±0.25	0.75±0.07	0.149

For the women treated with LMWH, the mean value of S/D ratio of fetal umbilical artery before and after LMWH treatment was respectively 3.26± 0.84 and 2.25 ±0.25. For the women treated with FRT, the mean value of S/D ratio of fetal umbilical artery before and after treatment was respectively 3.07± 0.86 and 2.93 ±0.66. For the women treated with LMWH+FRT, the mean value of S/D ratio of fetal umbilical artery before and after treatment was respectively 3.12±1.16 and 2.60±0.76. Among all the indexes, only the S/D ratio of fetal umbilical artery p=0.000 ($P \leq 0.05$) has statistical significance; In other indexes, P-value was more than 0.05, which has no statistical significance.

Table 7: Demographic and clinical characteristics of study patient after treatment (outcomes of the study)

Indices	Cases (n = 60)	Controls(n=60)	P-value
GA at Delivery (weeks)	36.07±2.881	38.23±1.332	0.000
GA (≥42weeks)	0(0)	0(0)	-
GA (37-41+6weeks)	35(58.3)	54(90)	0.000
GA (34-36+6weeks)	14(23.3)	6(10)	0.000
GA (<34week)	11(18.3)	0(0)	0.000
Delivery Mode, CS (%)	49(81.7)	45(75)	0.253
Delivery Mode, SVD (%)	11(18.3)	15(25)	0.253
Fetal weight at Delivery (g)	2419±764.29	3277±33	0.000
Normal birth weight: ≥2500g (%)	31(51.7)	60(0)	0.000
Low birth weight :< 2500g (%)	29(48.3)	0(0)	0.000
Neonate respiratory (Autonomous)	58(98.3)	59(98.3)	0.368
Neonate respiratory (Artificial)	0(0)	1(1.7)	0.368
Neonate respiratory (None)	1(1.7)	0(0)	0.368
APGAR Score at 1 minute	7.350±1.46	7.950±0.22	0.001
APGAR Score at 5 minutes	8.433±1.44	8.983±0.13	0.004
APGAR Score (≥8) (%)	42(70)	57(95)	0.001
APGAR Score (6-7) (%)	10(16.7)	3(5)	0.001
APGAR Score (<6) (%)	8(13.3)	0(0)	0.001
Normal amniotic fluid (%)	53(88.3)	56(93.3)	0.264
Abnormal amniotic fluid (%)	7(11.7)	4(6.7)	0.264
Neonatal asphyxia, No (%)	56(93.3)	60(0)	0.049
Neonatal asphyxia, yes (%)	4(6.7)	0(0)	0.049
Neonates (Full-term) (%)	35(58.3)	56(90)	0.001
Neonates (Preterm) (%)	24(40)	6(10)	0.001
Neonates (Stillbirth) (%)	1(1.7)	0(0)	0.001
NICU admission, No (%)	37(61.7)	57(95)	0.000
NICU admission, Yes (%)	23(38.3)	3(5)	0.000
Normal umbilical cord (%)	37(61.7)	44(73.3)	0.124
Cord round on the neck (%)	15(25)	16(26.7)	0.124
Cord tightly twisted (%)	2(3.3)	0(0)	0.124
Jelly umbilical cord (%)	2(3.3)	0(0)	0.124
Short umbilical cord (%)	1(1.7)	0(0)	0.124
Mixed umbilical cord lesions (%)	3(5)	0(0)	0.124
Placental lesions (%)	4(6.7)	1(1.7)	0.182
Newborn malformations (%)	8(13.3)	7(11.9)	0.514

From the study outcomes in Table 7, GA at Delivery(in weeks), Fetal weight at delivery(g), Normal and low fetal weight(%), APGAR score at 1 minute, APGAR Score at 5 minutes, APGAR Score staging, Full-term, Preterm, and stillbirth Neonates, Neonatal asphyxia, and NICU admission had all a p-value≤0.05, thus implying that they were statistically significant. However, for the rest of the variables, the p-value was greater than 0.05 indicating, that they were not statistically significant.

The mean values of fetal and maternal outcomes of pregnant women diagnosed with placental insufficiency and treated with drugs in the case group were compared with those in the normal control group: the gestational weeks of delivery in the case group were 36.07 ± 2.881 weeks, and those in the control group were 38.23 ± 1.332 weeks. Women delivered by CS were 49

cases (81.7%) in the case group and 45 cases (75%) in the control group. Women with SVD were 11 cases (18.3%) in the case group and 15 cases (25%) in the control group. Full-term neonates were 35 cases (58.3%) in the case group and 56 cases (90%) in the control group. Preterm neonates were 24 cases (40%) in the case group and 6 cases (10%) in the control group. Stillbirths were 1 case (1.7%) in the case group and 0 cases (0%) in the control group. SGA neonates (birth weight :< 2500g) were 29 cases (48.3%) in the case group and 0 case (0%) in the control group. AGA neonates (birth weight: ≥ 2500g) were 31 cases (51.7%) in the case group and 60 cases (0%) in the control group. Neonates with an Apgar score (≥ 8 points) were 42 cases (70%) in the case group and 57 cases (95%) in the control group. Neonates with an Apgar score (6 -7 points) were 10 cases (16.7%) in the case group and 3 cases (5%) in the control group. Neonates with an Apgar score (<6 points) were 8 cases (13.3%) in the case group and 0 cases (0%) in the control group. Neonates with asphyxia were 4 cases (6.7%) in the case group and 0 (0%) in the control group. Neonates admitted in NICU were 23 cases (38.3%) in the case group and 3 cases (5%) in the control group.

Discussion

Fetal hemodynamic and placental function monitoring depend on diagnostic methods, among which Doppler ultrasound has become a noninvasive, and rapid examination method to detect early hemodynamic changes, which is used for early detection of fetal and maternal complications. Modern studies have also proved that systematic application of Doppler ultrasound can reduce the perinatal mortality of pregnancy with late placental insufficiency by about 50% [48].

Doppler ultrasound was a procedure chosen before and after drugs administration, which was used to monitor the fetal placental blood circulation parameters to judge the efficacy of the placental insufficiency drugs (LMWH, FRT, and LMWH + FRT), and to prevent adverse fetal and maternal outcomes [49]. Doppler ultrasound has shown the precise effect in the diagnosis, surveillance, and prognosis of pregnancies complicated placental insufficiency [50].

In our study, we performed a clinical study, on the effectiveness of S/D ratio of the fetal umbilical artery as one of the Doppler ultrasound blood flow indices for detecting placental insufficiency. The mean S/D ratio for the case and control groups was respectively 60(100%)) and 0(0%) with p-value=0.000, which was statistically significant, as shown in the Table 1. Moreover, the mean S/D ratio of fetal umbilical artery in case group and control group was respectively 3.46±0.45 and 2.18 ±0.34, P-value=0.000, had statistical significance before treatment; and was respectively 2.57 ±0.76 and 2.29 ±0.34, P-value=0.000 was statistically significant too after treatment, which indicates that the S/D ratio of the fetal umbilical artery as one of the Doppler ultrasound blood flow indices has significant significance in the evaluation of placental insufficiency [34, 38].

We also found that, for the **women treated with LMWH,** the mean value of S/D ratio of fetal umbilical artery before and after LMWH treatment was respectively 3.26± 0.84 and 2.25 ±0.25; the mean value of S/D in the fetal umbilical artery before and after treatment was significantly different, which indicated that LMWH alone had a certain effect on improving fetal umbilical blood flow [39, 40]. For the **women treated with FRT**, the mean value of S/D ratio of fetal umbilical artery before and after treatment was respectively 3.07±0.86 and 2.93 ±0.66; there was no significant difference in the mean value of S/D ratio between the two groups before and after treatment, indicating that the effect of FRT alone was not good, and was not as effective as other drugs [33, 42, 43]. For the **women treated with LMWH+FRT**, the mean value of s/d ratio of fetal umbilical artery before and after treatment was respectively 3.12±1.16 and 2.60 ±0.76; the mean value of S/D in fetal umbilical artery before and after treatment was significantly different, which indicates that LMWH + FRT was more effective than single FRT, and the effect was similar to that of LMWH alone [38, 41].

From to the results of the cross tables 4, 5 and 6, the average value of S/D ratio of fetal umbilical artery improved after the use of drugs, and the P-values (P =0.000, P≤0.05) in both cases were statistically significant, which indicates that drug therapy was effective in improving the S/D ratio as Doppler ultrasound blood flow indexes of pregnant women with placental insufficiency in late pregnancy [50].

Our results show that LMWH can significantly improve the S/D ratio of fetal umbilical artery in patients with placental insufficiency in late pregnancy, suggesting that it has a good therapeutic effect. But it was not helpful for the indexes of PS, PI, RI, and so on; FRT alone has little significance in reducing the ratio of S/D of the fetal umbilical artery, which suggests that the treatment effect is not good; The S/D ratio of fetal umbilical artery in patients with placental insufficiency in late pregnancy can also be significantly reduced by LMWH + FRT; This means that LMWH and LMWH + FRT are more effective in the treatment of placenta insufficiency in late pregnancy [34, 35]. However, based on the difference between the mean value of Doppler ultrasound blood flow indices before and after treatment, we can say that the drugs did not show full effectiveness in treating placental insufficiency [34].

According to the difference of the mean value of Doppler ultrasound indices before and after treatment, as shown in Tables 4, 5, and 6, it can be said that drug treatment of late placental insufficiency and improvement of its Doppler ultrasound indexes was effective, but it could not make it return to normal [29]. Due to the limited number of cases, it was not also clear which drug regimen is more significant for improving the above indicators, therefore, further studies are needed to observe its effect [34, 38].

Furthermore, Comparing to the healthy women in the control group, the mean value of fetal and maternal outcomes of patients with late placental insufficiency in the control group was mostly low as shown in Table7; these data indicate that pregnancies complicated with late placental insufficiency are often associated with fetal and maternal adverse outcomes [27]. We found that pregnant women with late placental insufficiency in the case group showed a variety of adverse neonatal and maternal outcomes during delivery, such as premature delivery, low fetal weight at delivery, small gestational age at delivery (<37weeks), low Apgar score at delivery (< 6 points), etc.

We also found that the incidence of premature labor, cesarean section, abnormal amniotic fluid, abnormal placental morphology, abnormal umbilical cord, low birth weight (< 2500g), neonatal asphyxia, stillbirth, and NICU admission was higher in the case group than in the normal control group, we can prove from these data that the adverse outcomes of fetus and mother are related to single pregnancy with late placental insufficiency [29, 50].

Conclusion

Low-molecular-weight heparin (LMWH) alone or a combination of low-molecular-weight heparin and fluids replacement therapy(LMWH + FRT) as a potential treatment of placental insufficiency in the third trimester of single pregnancies can

significantly reduce the S/D ratio of the fetal umbilical artery, suggesting that, it has a significant effect on the improvement of placental function. Moreover, fetal and maternal adverse pregnancy outcomes were associated with placental insufficiency in the third trimester of single pregnancies.

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