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# ASSESSMENT OF CARDIAC SPARING EFFECT IN INTRAUTERINE GROWTH RESTRICTED FETUSES: A PROSPECTIVE COHORT STUDY

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**Abstract**
Objective: The study aimed to find a difference in the cardiac output (COP) between normal and intrauterine growth restricted (IUGR) fetuses and to clarify a heart-sparing effect in IUGR fetuses (a new issue).
Material and methods: This single-center, prospective cohort study, was conducted at Assiut Woman's Health University Hospital, Egypt, prospectively registered at clinical trial.gov NCT03146507. Two hundred and ten women were included: women with normal pregnancy (Group A:N=105) and women whose pregnancy was complicated by IUGR between 32 to 34 weeks gestation(Group B:N=105) from 2017 to 2022. Women underwent fetal Doppler echocardiography, umbilical (UA), and middle cerebral (MCA) artery Doppler assessment. The primary outcome included the relative cardiac output ratio at 32-34 weeks. Changes in Doppler indices in the UA and MCA were also recorded. Data were analyzed by unpaired Student's t-test and Chi-square test.
Results: At 32-34 weeks and from 34 to 36 weeks; there was a higher value of right-side cardiac output in group A compared with group B; with a statistically significant difference (p=<0.001). While; the left-sided cardiac output was comparable in both groups; it was significantly higher in the IUGR group from 34 to 36 weeks.
Conclusion: There are significant changes in the cardiac output in IUGR fetuses in late pregnancy as compared with normal pregnancy thus confirming the hypothesis of heart sparing phenomenon.
Keywords: Cardiac Sparing, Fetal Hypoxia, IUGR, Fetal Echocardiography, umbilical artery Dopple

## Introduction

The fetal cardiovascular system undergoes significant changes in response to hypoxia. These changes involve adjustments to the heart rate, an elevation in arterial blood pressure, and a redistribution of the cardiac output to prioritize vital organs. These adaptive reactions play a crucial role in maintaining fetal homeostasis (1). There are three subtypes of hypoxic pregnancy conditions: pre placental hypoxia, utero placental hypoxia, and post placental hypoxia. In the latter, only the fetus experiences hypoxia (2).

A foetus with intrauterine growth restriction (IUGR) weighs below the 10th percentile for their gestational age (3). Insufficiency of the placenta causes chronic hypoxia and intrauterine growth limitation. The fetal heart also helps adjust to hypoxemia and placental insufficiency. IUGR's hemodynamic cascade begins with anomalies in the umbilical and middle cerebral arteries (UA and MCA). Placental dysfunction affects the heart and causes hemodynamic alterations (6, 7). UA increases and MCA blood-flow resistance decreases during circulatory adaptation (8).

Doppler monitoring of IUGR is successful (9). Arterial Doppler anomalies are followed by right cardiac diastolic, systolic, and left cardiac indices [11, 12].

Maintaining left ventricular output requires preserving left systolic function until it becomes aberrant. This is crucial for cerebral and coronary blood flow. Late in pregnancy, the fetal cardiovascular system reduces oxygen consumption and redirects cardiac output from peripheral vascular beds to essential circulations like brain perfusion. Redistribution of blood flow to the fetal brain is called the 'brain-sparing effect' (10). Doppler ultrasound helps assess cardiovascular problems in at-risk pregnancies. Sometimes it may protect the heart, according to research. Fetal blood redistribution severity suggests fetal adaptability and pregnancy safety (11, 12).

This study aimed to address the difference in the COP between normal and IUGR fetuses and to explain the heart sparing effect in IUGR fetuses

## Patients and Methods:

This study was conducted at a single center and involved a prospective cohort. The study was conducted from August 1, 2017 to February 1, 2021, following approval from the Ethical Committee of Assiut University Hospitals in Egypt (IRB54256). The study was registered at Clinical trial.gov: (NCT03146507). The study involved a group of pregnant women, specifically those between the ages of 20 and 35, with a BMI ranging from 20 to 30 kg/m2. These women were in the later stages of pregnancy, between 32- and 34-weeks gestation, and were carrying a single baby. We enrolled both healthy pregnant women and women with late intrauterine growth restriction (IUGR). This condition is characterized by a lower estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile (13). At the time of recruitment, the pulsatility index (PI) in the umbilical arteries of those women exceeded the 95th percentile.

Premature pre-labor rupture of membranes, antepartum hemorrhage, fetal congenital anomalies, absent or reversed umbilical artery diastolic flow at recruitment, preeclampsia, anti-coagulant medication, and refusal to participate were exclusion criteria.

A total of 251 women received counseling for potential participation, but unfortunately, 41 women were unable to be included in the study. The reasons for exclusion varied, with 14 women having hypertension, 9 women taking aspirin during pregnancy, 10 women having placenta previa, and 8 women choosing not to participate. Therefore, a total of 210 women agreed to take part in the study, and they were evenly split into two groups. Group A consisted of 105 healthy pregnant women, while group B comprised 105 women with IUGR.

Interestingly, in group A, there was a loss of 31 women from follow up, whereas in group B, 24 women were lost from follow up. Additionally, 4 women in group B experienced IUFD, and 7 women developed absent/reverse diastolic flow. After careful analysis, the data from 74 women patients in group A and 70 women in group B were considered.

Every patient underwent a thorough process of gathering their medical history, conducting a comprehensive clinical examination, performing ultrasound scans, and utilizing fetal Doppler echocardiography.

**Ultrasound examination**

Baseline assessment of gestational age, amniotic fluid index, and fetal weight were done. The fetal weight was calculated based on Hadlock-4 formula (14). UA and MCA were measured (15). All ultrasound examinations were done using a Medison X8, machine at Assiut University; Women Health Hospital Advanced Fetal Medicine Unit.

**Fetal Doppler echocardiography**

A thorough fetal echocardiogram included nine cardiac views (16). Left and right stroke volumes were calculated using the aortic or pulmonary valve diameter and systolic flow velocity-time integral, using the formula $\pi/4*(\text{diameter})^2*$ (flow velocity –time integral). During systole, frozen real-time images were used to quantify aortic and pulmonary valve sizes using the leading edge to edge approach. An apical or basal 5 chamber view of the heart captured aortic systole flow, while a right ventricle outflow tract view captured pulmonary artery flow. The velocity time integrals were calculated by manually tracing the spectral Doppler area. Left and right cardiac outputs were calculated by multiplying stroke volume by fetal heart rate. Thus, the relative cardiac output—the ratio of the right and left cardiac outputs—was calculated. Software in the ultrasound machine took the measurements automatically.

So that we used the following definitions:

Right cardiac output= $\pi/4*(\text{pulmonary valve diameter})^2*$ (pulmonary artery systolic flow velocity –time integral)*heart rate

Left cardiac output= $\pi/4*(\text{aortic valve diameter})^2*$ (aortic artery systolic flow velocity –time integral) *heart rate

Cardiac output ratio=(ratio between right side cardiac outputs to left side cardiac output)

**Follow-up**

During each visit, women underwent a clinical assessment and were inquired about the adequacy of fetal movement. As part of the evaluation process, women underwent regular clinical assessments. Additionally, their fetal weight was measured every two weeks using 2D ultrasound. The blood flow in the umbilical arteries and MCA was also evaluated twice a week using Doppler technology.

A Fetal Doppler echocardiography was performed to determine the ratio of cardiac output between the right and left sides of the heart at 34-36 weeks. A CTG was performed for women who reported decreased fetal movement after 32 weeks. A course of corticosteroids was administered during the 34th and 36th week of pregnancy.

In group A, routine antenatal care was provided. During the follow-up visits, various measurements were taken including fetal weight, umbilical, middle cerebral artery, and cardiac ratio. These measurements were recorded both at the time of recruitment and at 34-36 weeks. During delivery, the medical team documented the outcomes for both the mothers and their babies, comparing those with intrauterine growth restriction (IUGR) to those with normal fetal development.

**Final participant status**

By the end of the study, the final status of the participants was classified as “completed study” or “lost to follow up”. Termination of pregnancy after corticosteroid was offered to whenever women had an indication for delivery. Women whose fetuses died during follow-up visits were also excluded.

**The study outcomes**

The main focus of the study was to determine the ratio of cardiac output between the right and left sides of the heart at 32-34 weeks. The study also examined several additional factors, including the ratio of cardiac output at 34-36 weeks, the pulsatility index in the umbilical artery and MCA at 32-34 weeks and 34-36 weeks, the MCA/UA PI ratio at 32-34 weeks and 34-36 weeks, the timing of delivery in weeks, birth weight in grams, mode of delivery, Apgar score at five minutes, the number of term/preterm babies, the number of stillbirths, and the number of babies admitted to the NICU.

**Sample Size Calculation:**

The sample size calculation was determined by considering the primary outcome, which is the relative cardiac output ratio. A recent study conducted by Mielke G et al., 2020 revealed an interesting finding regarding the ratio of right (60%) to left cardiac output (40%), which was found to be approximately 1.5 (18). Assuming that, like the brain sparing phenomenon seen in late FGR, there is increased blood flow within the MCA, we can hypothesize that the cardiac ratio may be reversed. This means that there may be increased cardiac output (COP) in the left ventricle compared to the right side, in order to meet the increased blood needs of the fetus. Based on statistical analysis, a sample size of 210 patients (105 in each group) is recommended to achieve a power of 80% in detecting a 50% difference between the two groups. This calculation takes into account a rate of loss to follow-up of 10%.

**Statistical analysis**

Statistical analysis was done with SPSS v26 (IBM Inc., Chicago, IL, USA). The two groups' quantitative variables' mean and SD were compared using an unpaired Student's t-test. Qualitative factors were analyzed using frequency and percentage. An appropriate Chi-square or Fisher's exact test was utilized for analysis. Two-tailed P values under 0.05 were statistically significant.

**Results**

Both groups were similar in baseline socio-demographic and obstetrics data without statistically significant differences **(Table 1)**.

**Table 1: Demographic data and obstetric history of the studied groups**

Data are presented as Mean ± SD and number (%) or Median (IQR)

| | | Normal group (n=105) | IUGR group (n=105) | P value |
|---|---|---|---|---|
| **Age (years)** | | 29.05 ± 4.59 | 28.38 ± 3.99 | 0.265 |
| **Residency** | **Urban** | 48 (45.71%) | 42 (40%) | 0.403 |
| | **Rural** | 57 (54.29%) | 63 (60%) | |
| **Education** | **Illiterate** | 31 (29.52%) | 29 (27.62%) | 0.856 |
| | **Basic** | 41 (38.68%) | 40 (37.74%) | |
| | **Secondary or more** | 32 (30.48%) | 36 (34.29%) | |
| **Employment** | | 45 (42.86%) | 46 (43.81%) | 0.889 |
| **Parity** | **0** | 16 (15.24%) | 24 (22.86%) | 0.053 |
| | **1** | 24 (22.86%) | 11 (10.48%) | |
| | **2 to 3** | 44 (41.9%) | 53 (50.48%) | |
| | **More than 3** | 21 (20%) | 17 (16.19%) | |
| **Number of living children** | **1** | 22 (20.95) | 12 (11.43) | 0.856 |
| | **2 to 3** | 33 (31.43) | 34 (32.38) | |
| | **More than 3** | 33 (31.43) | 35 (33.33) | |
| **BMI (kg/m$^2$)** | | 27.90 ± 3.17 | 28.68 ± 3.95 | 0.116 |
| **Obstetric history** | | | | |
| **Parity** | **0** | 16 (15.24%) | 24 (22.86%) | 0.053 |
| | **1** | 24 (22.86%) | 11 (10.48%) | |
| | **2 to 3** | 44 (41.9%) | 53 (50.48%) | |
| | **More than 3** | 21 (20%) | 17 (16.19%) | |
| **Number of living children** | **1** | 22 (20.95%) | 12 (11.43%) | 0.856 |
| | **2 to 3** | 33 (31.43%) | 34 (32.38%) | |
| | **More than 3** | 33 (31.43%) | 35 (33.33%) | |
| **History of previous abortion** | | 21 (20%) | 30 (28. 5%) | 0.148 |
| **Previous route of delivery** | **VD** | 40 (38.1) | 30 (28.57) | 0.267 |
| | **CS** | 48 (45.71) | 51 (48.57) | |
| **Duration from last pregnancy (years)** | | 2.6 (1.9 -3.4) | 1.5 (1-2) | 0.799 |
| **Gestational age at the time of recruitment (weeks)** | | 32.7 ± 0.5 | 32.66 ± 0.45 | 0.602 |

**BMI** Bod mass index, **IUGR** Intra-uterine growth restriction, **CS** Cesarean section, **VD** Vaginal delivery

As regards the EFW, there was a significant difference between both groups in 32-34 weeks and > 34-36 weeks (p=<0.001; respectively). Moreover, there was a lower PI in the UA and higher PI in the MCA in group I in comparison with group II with significant difference (p<0.001). Also, a higher UA -PI / MCA -PI Ratio was reported in group I (p<0.001) **(Table 2).**

**Table 2: EFW and Doppler indices in both groups**

| Mean ± SD | Normal group (n=105) | IUGR group (n=105) | P value |
|---|---|---|---|
| **32-34 weeks** | | | |
| **EFW (g)** | 1864.09 ± 116.17 | 1190.77 ± 116.36 | **<0.001*** |
| **UA -PI** | 1.11 ± 0.11 | 1.46 ± 0.09 | **<0.001*** |
| **MCA -PI** | 1.5 ± 0.14 | 1.16 ± 0.06 | **<0.001*** |
| **MCA -PI / UA -PI Ratio** | 1.37 ± 0.18 | 0.79 ± 0.06 | **<0.001*** |
| **> 34-36 weeks** | | | |
| **EFW (g)** | 2583.83 ± 234.38 | 1580.98 ± 132.93 | **<0.001*** |
| **UA –PI** | 1.09 ± 0.14 | 1.5 ± 0.1 | **<0.001*** |
| **MCA-PI** | 1.33 ± 0.13 | 1.02 ± 0.1 | **<0.001*** |
| **MCA -PI / UA -PI Ratio** | 1.27 ± 0.52 | 0.69 ± 0.08 | **<0.001*** |

**EFW** Estimated fetal weight, **IUGR** Intra-uterine growth restriction, **g** gram, **MCA** Middle cerebral artery, **PI** Pulsatility index, **UA** Umbilical artery

* Statistically significant difference (P < 0.05).

At 32-34 weeks; right side cardiac output (388.93 ± 92.27) in group A was higher in comparison to group B (345.46 ± 60.52) with statistically significant difference (p=<0.001). However; the left side cardiac output was comparable in both groups (355.58 ± 86.82 Vs. 375.42 ± 68.34, p=0.067; respectively). Lastly, there was a statistically significant difference between both groups regards COP ratio (1.1 ± 0.11 vs. 0.92 ± 0.09, p=<0.001; respectively) **(Table 3).**

Table 3: COP at gestational age 32-34 weeks and > 34-36 weeks in both groups

| **Mean ± SD** | **Normal group (n=105)** | **IUGR group (n=105)** | **P value** |
|---|---|---|---|
| **32-34 weeks** | | | |
| **Right side cardiac output** | 388.93 ± 92.27 | 345.46 ± 60.52 | **<0.001*** |
| **Left side cardiac output** | 355.58 ± 86.82 | 375.42 ± 68.34 | 0.067 |
| **COP ratio** | 1.1 ± 0.11 | 0.92 ± 0.09 | **<0.001*** |
| **> 34-36 weeks** | | | |
| **Right side cardiac output** | 524.66 ± 82.66 | 455.89 ± 74.26 | **<0.001*** |
| **Left side cardiac output** | 456.82 ± 93.71 | 482.94 ± 75.82 | **0.048*** |
| **COP ratio** | 1.17 ± 0.13 | 0.96 ± 0.12 | **<0.001*** |

**COP** Cardiac output, **IUGR** Intra-uterine growth restriction
* Statistically significant difference (P < 0.05).

From 34 t0 36 weeks; there was also a higher figure of right-sided cardiac output in normal pregnant group (524.66 ± 82.66) in comparison to IUGR group (455.89 ± 74.26) with statistically significant difference (p=<0.001). The left side cardiac output also showed a statistically significant difference between groups at 34-36 weeks (p=0.048). Finally, there was a statistically significant difference between both groups regards COP ratio (1.17 ± 0.13 vs. 0.96 ± 0.12, p=<0.001; respectively) **(Table 3).**
As regards the pregnancy and neonatal outcomes; the gestational age at time of delivery and the birth weight was significantly higher in group A in comparison to group B with statistically significant difference (P=<0.001). There is also a significant difference between both groups in the mode of delivery in the current pregnancy (P= 0.002). However, there was insignificantly difference was noted between groups in the number of term and preterm babies (p= 0.529). A higher number of babies with Apgar score >7 was noted in group A, while more babies were admitted to NICU in group B (p<0.001). More days were needed for babies in NICU in the group II with a higher number of neonatal mortality (p= 0.004, p=.003) **(Table 4).**

Table 4: Pregnancy and neonatal outcomes of the studied groups

| | | **Normal group (n=74)** | **IUGR group (n=70)** | **P value** |
|---|---|---|---|---|
| **GA at time of delivery (weeks)** | | 38.24 ± 1.02 | 37.53 ± 0.62 | **<0.001*** |
| **Mode of delivery in the current pregnancy** | | | | |
| VD after spontaneous onset of labor | | 29 (39.19%) | 10 (14.29%) | **0.002*** |
| VD after induction of labor | | 8 (10.81%) | 10 (14.29%) | |
| Planned CS | | 32 (43.24%) | 35 (50%) | |
| CS for fetal distress after induction | | 5 (6.76%) | 15 (21.43%) | |
| **Birth weight (g)** | | 3230.66 ± 87.64 | 1947.2 ±126.49 | **<0.001*** |
| **Time of termination** | Term | 66 (89.19%) | 60 (85.71%) | 0.529 |
| | Preterm | 8 (10.81%) | 10 (14.29%) | |
| **Apgar score >7** | | 49 (46.67%) | 26 (24.76%) | **<0.001*** |
| **Admission at NICU** | | 8 (7.62%) | 35 (33.33%) | **<0.001*** |
| **Neonatal hospital stays (days)** | | 2.13 ± 0.83 | 4.03 ± 1.7 | **0.004*** |
| **Mortality at NICU** | | 1 (0.95%) | 11 (10.48%) | **0.003*** |

Data are presented as Mean ± SD or number (%).
**CS** Caesarian section, **GA** Gestational age, **IUGR** Intra-uterine growth restriction, **VD** Vaginal delivery, **g** Gram, **NICU** Neonatal intensive care unit
* Statistically significant difference (P < 0.05).

**Discussion**
This study found that normal pregnant women have higher right side COP than IUGR women. IUGR patients had increased left side COP during weeks 34–36. The cardiac sparing phenomenon was proven by the right side's decreased cardiac output pressure and the left side's increased pressure in intrauterine growth restriction.
Interesting discoveries have been found in fetal circulatory studies in intrauterine growth retardation and hypoxia. These studies reveal that umbilical artery flow resistance increases during fetal circulation redistribution. In particular, the internal carotid and middle cerebral arteries decrease resistance and enhance velocity, while the descending thoracic aorta does the opposite (19). Pulsations in the umbilical vein and increased reverse flow from the right atrium into the inferior vena cava when the atrium contracts suggest cardiac dysfunction and heart failure in cases of high placental resistance (20).

Our investigation shows a significant right-left cardiac output difference in group I. This supports prior findings showing that the fetal heart favors the right ventricle in late pregnancy, with this dominance increasing (20).

Group II (IUGR) fetuses had a significant differential in left cardiac output. Since LCO, RCO, and CCO reflect afterload conditions, this discrepancy exists. Fetuses with IUGR have lower cardiac outputs and decreased blood flow due to increased left ventricle stroke volume. During pregnancy, the right ventricle rules. For fetuses with growth constraints, Figueras et al. (20) found that major artery maximum velocities changed with delivery time. Mäkikallio et al. (20) evaluated umbilical biochemical markers of heart dysfunction in IUGR babies. Interestingly, fetuses with different markers had similar cardiac output. Bahtiyar and Copel (20) found that IUGR fetuses have the same CCO as typically developed ones.

Mari et al. (21) found that therapeutic therapy for IUGR focuses on waveform analysis, particularly the PI. Low PI suggests cardiac output to brain transfer. Saha et al. (22) observed that MCA peak systolic velocity (PSV) is usually used to predict and treat newborn anemia. In IUGR babies, a greater MCA-PSV level predicted perinatal death better than a lower MCA-PI level. Monitor at-risk fetuses with regular Doppler measurements like the MCA.

Compared to the IUGR group, the control group had significantly lower PI in the UA and higher PI in the MCA ($p<0.001$). The IUGR group had a considerably higher UA-PI/MCA-PI Ratio ($p<0.001$).

Ashwal et al. (23) found that MCA Doppler detected more pathologies, supporting our findings. According to Rizzo et al. (2008), group C had considerably lower PI readings from the UA than group A ($P < 0.0001$) (7).

In group I neonates, MCA PI values below the 5th percentile were highly suggestive of poor 1-minute Apgar scores, according to Moawad, E.M.I. et al. (24). The study has 73.2% sensitivity and 87% NPV. According to Abdelrazik et al. (25), babies with poor outcomes have lower middle cerebral artery PI indexes.

The IUGR group had significantly lower EFW than the control group. Cruz-Lemini et al. (25) found that IUGR patients had lower estimated fetal weight and fetoplacental Doppler parameters, supporting our findings. According to Comas et al. (26) the IUGR group had a significantly lower estimated fetal weight than the control group.

Compared to the IUGR group, the control group had a substantially greater gestational age at birth ($38.24 \pm 1.02$ vs. $37.53 \pm 0.62$). Zakaria et al. (27) found that patients had considerably lower GA than controls, supporting our findings. Sukgen and Kaya (28) confirmed our findings that the control group had a higher gestational age at birth than the IUGR group. The control and IUGR groups also differed in current pregnancy delivery technique ($P= 0.002$). Cruz-Lemini et al. (29) found that IUGR patients had higher Caesarean delivery rates than controls. Similar to Comas et al. (30), IUGR pregnancies had greater rates of cesarean delivery, perinatal mortality, and worse outcomes than the control group.

The control group had a significantly greater birth weight than IUGR. No statistical difference was seen between groups at termination. In the control group, more newborns had Apgar scores over 7. Similar to our findings, Zakaria et al. (27) observed that cases had lower birth weight and APGAR ratings at 1 and 5 minutes than controls. Sukgen and Kaya (28) found a link between low birth weight and IUGR, supporting our findings.

Additional days were required for infants in the NICU within the IUGR group, which experienced a higher rate of neonatal mortality ($p= 0.004$, $p=.003$). Consistent with our findings, Zakaria et al. (27) discovered that the amount of time spent in the NICU was significantly longer for cases compared to controls. Sengodan and Mathiyalagan (31) proposed that certain factors, such as the requirement for NICU admission, the duration of NICU stay, and perinatal mortality, should be considered.

Sukgen and Kaya (32) found contrasting results to ours, indicating that there was no statistically significant correlation between the IUGR group and control group in terms of 1st and 5th minute Apgar scores and NICU needs of newborns ($p>0.05$). It's possible that the variation is due to varying sample sizes.

Points of strength of this study: This is the first study that estimated the role of cardiac output ratio in prediction of fetal heart sparing in IUGR practically. Noninvasive and quantitative tool in assessment of hemodynamic changes related to fetal hypoxia. Sample size of this study (210) is considered satisfactory as launching research to delineate the difference between the two study groups. Establishment of methodology for fetal COP measurement is a good practical point.

Points of weakness: It was a single center study. The value of cardiac sparing effect is questionable as it has no implication on timing of delivery. Difficult maneuver should be carried out by fetal echocardiography specialist. The availability of other diagnostic Doppler ultrasound tools that can assess the hemodynamic changes of fetal hypoxia. Also; the study's findings may not be applicable to other centers, particularly if they lack a specialized obstetric ultrasonography center where obstetricians do prenatal ultrasound exams. The short period of follow-up was also a limitation.

**Conclusions:**

The cardiac output in IUGR fetuses differs significantly in IUGR fetuses at the late pregnancy from normal pregnancy. The right side COP becomes higher than left side in those fetuses indicating the cardiac sparing phenomenon.

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