

Evaluation of cerebroplacental ratio as a new tool to predict adverse perinatal outcomes in patients with isolated oligohydramnios

Serebroplasental oranın izole oligohidroamniyoslu hastalarda kötü perinatal sonuçların öngörülmesindeki yeri

Emre Destegül¹, Hatice Akkaya², Barış Büke³, Güliz Güler⁴

¹ Niğde Ömer Halisdemir University Medical Faculty Training and Research Hospital Department of Obstetrics and Gynecology, Niğde, Turkey

² Ankara City Hospital Training and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

³ Private BB, Obstetric & Gynecology Clinic, İzmir, Turkey

⁴ Niğde Ömer Halisdemir University Medical Faculty Training and Research Hospital Department of Pediatrics, Niğde, Turkey

ORCID ID of the author(s)

ED: 0000-0001-5726-0223

HA: 0000-0002-9613-1712

BB: 0000-0001-8761-2023

GG: 0000-0003-2922-430X

Corresponding author/Sorumlu yazar:
Emre Destegül

Address/Adres: Niğde Ömer Halisdemir Üniversitesi Rektörlüğü, Merkez Kampüs, Bor Caddesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Niğde, 51240, Türkiye
E-mail: destegulemre@hotmail.com

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Abstract

Aim: There is conflicting information in the literature regarding perinatal outcomes and management of isolated oligohydramniotic (IO) pregnancies. Recent studies show that IO is associated with poor perinatal outcomes. However, there is still no definitive method for deciding the optimal delivery timing for these patients. In this study, we aimed to assess the relationship between Doppler parameters, especially cerebro-placental ratio, and perinatal outcomes in isolated oligohydramnios (IO) patients.

Methods: This prospective case control study was conducted between October-November 2018. A total of 98 patients were recruited and divided into two groups, as pregnant women with normal amounts of amniotic volume and the isolated oligohydramnios group. Oligohydramnios diagnosis was made by amniotic fluid index measurement (AFI<5 cm). Pregnancies with hypertension, fetal growth restriction, thrombophilia, preeclampsia, diabetes mellitus, preterm births and chromosomal/structural abnormalities were excluded. Cerebro placental ratios of groups were compared in terms of composite adverse outcomes, low APGAR score in 1st and 5th minutes, C/S operation due to non-reassuring fetal heart rate patterns, admission to neonatal intensive care unit and still births.

Results: In the isolated oligohydramnios group (n=45) cerebro-placental ratio (CPR) was lower compared to control group ($P<0.001$). IO was associated with lower (APGAR score<7) 1st (55.6% vs. 7.5%, $P<0.001$) and 5th (13.3% vs. 1.9% $P=0.028$) minute APGAR scores and higher rates of NICU admission (26.7% vs. 3.8% $P=0.001$). Number of fetal distress cases was higher in patients with low CPR in the IO group (9 vs. 6 $P=0.023$).

Conclusion: Measurement of CPR among IO patients seems useful for detection of fetuses with higher risk for poor neonatal outcomes.

Keywords: Cerebroplacental ratio, CPR, Isolated oligohydramnios, Perinatal outcome, Fetal Doppler

Öz

Amaç: İzole oligohidramniotik (IO) gebeliklerin perinatal sonuçları ve yönetimi ile ilgili literatürde hala çelişkili bilgiler mevcuttur. Son çalışmalarda ise IO'nun kötü perinatal sonuçlar ile ilişkili olduğu yönündedir. Yine de bu hastaların optimal doğum zamanlamasına karar vermek için elimizde hala kesin bir yöntem bulunmamaktadır. Biz de çalışmamızda IO hastalarında Doppler parametreleri, özellikle serebro-plasental oran ve perinatal sonuçlar arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Bu prospektif vaka kontrol çalışması Ekim-Kasım 2018 arasında gerçekleştirildi. Çalışmaya 98 hasta dahil edilmiştir. İzole oligohidroamniyos ve normal amnion miktarı olan gebeler grubu olmak üzere iki gruba ayrıldı. Oligohidramnios tanısı amniyotik sıvı indeksi ölçümü ile konuldu (AFI <5 cm). Hipertansiyon, intrauterin büyüme kısıtlılığı, trombofilisi, preeklampsi, diyabet ve kromozomal / yapısal anormallikleri olan gebelikler çalışma dışı bırakıldı. Gruplar cerebroplasental oran (CPR) ölçümleri göz önüne alınarak; kompozit advers sonuçlar, 1. ve 5. dakikalarda düşük APGAR skoru, güven verici olmayan fetal kalp hızı paternlerine bağlı sezaryen (C/S) operasyonu, yenidoğan yoğun bakım ünitesine yatışı ve ölü doğumlar bakımından karşılaştırıldı.

Bulgular: CPR <1,08 olan hastalarda fetal distress görülme oranı daha yüksekti (9'a karşı 6 $P=0,023$). İzole oligohidramnios grubunda (n=45) CPR kontrol grubuna göre daha düşük saptandı. Ayrıca IO, daha düşük (APGAR <7) 1. (%55,6 ve %7,5, $P<0.001$) ve 5. (%13,3 ve %1,9, $P=0,028$) dakika APGAR skorları ve daha yüksek YYBÜ kabul oranları ile (%26,7 ve %3,8, $P=0,001$) ilişkili idi.

Sonuç: CPR ölçümü, IO hastalarında kötü neonatal sonuçlar açısından daha yüksek risk taşıyan fetüslerin saptanmasında yararlı görünmektedir.

Anahtar kelimeler: Serebroplasental oran, CPR, İzole oligohidramnios, Perinatal sonuç, Fetal Doppler

Introduction

The amniotic fluid volume being less than expected for gestational age is defined as oligohydramnios. Its incidence at term pregnancies ranges between 0.5-5% depending on measurement methods, patient population, and gestational age (GA) [1,2]. Definition of oligohydramnios is mostly performed by amniotic fluid index (AFI) <5cm and single deepest pocket (SDP) <2 cm. Adequate amniotic fluid is important for normal fetal growth, fetal lung development, and for protecting the fetus and umbilical cord from trauma.

Various conditions such as premature rupture of membranes, placental dysfunction, chromosomal and congenital abnormalities, and medications can cause oligohydramnios, or it may be isolated. It is well known that oligohydramnios, regardless of its etiology (except isolated oligohydramnios), is related to increased adverse perinatal outcomes, such as low APGAR scores, neonatal intensive care unit admission (NICU), meconium presence in amniotic fluid, meconium aspiration syndrome (MAS), and increased cesarean section ratings due to fetal distress [3-12].

Although data about the importance of isolated oligohydramnios (IO) in the literature is controversial, last reviews showed an increase in adverse perinatal outcomes such as increased cesarean delivery rates, low APGAR scores, and a higher rate of NICU admission [13-25].

Routine Antenatal Imaging with Ultrasound (RADIUS) trial reported that in IO patients, fetal growth did not deteriorate, but placental insufficiency could be present, even with growth percentiles higher than 10% [26]. Furthermore, Locatelli and colleagues reported an underlying fetal growth retardation in 13.2% of pregnancies with IO, which could not be detected before delivery [14].

On the other hand, The American College of Obstetricians and Gynecologists (ACOG) pointed out in 1999 that insufficient data was present for labor induction in IO. Therefore, ACOG did not declare a definitive statement regarding the optimal timing of delivery [27]. Despite this information, when an IO diagnosis is made in term pregnancies (beyond 37 weeks of GA) clinicians almost always lean towards induction of labor [28].

Evaluation of fetal vascular structures, maternal uterine artery circulation and amniotic fluid is widely used in the assessment of fetal well-being in contemporary obstetric practice. Umbilical artery (UA), middle cerebral artery (MCA), ductus venosus doppler have been used so far for assessment of fetal status. The cerebroplacental ratio (CPR), which was reported first in 1987 [29], represents the alteration of the blood flow towards the brain due to cerebrovascular dilatation. Also, an increase in placental bed resistance and decreased diastolic flow in the umbilical artery contribute to CPR. CPR can be calculated as MCA resistance index (RI) divided by UA resistance index or MCA pulsatility index (PI) divided by UA pulsatility index. We know that CPR measurement is more valuable than UA and MCA Doppler in pregnancies with fetal growth restriction (FGR) [30]. Also, near-term, detection of potential FGR can be difficult because of the imprecise evaluation of the fetal weight due to

intra and inter-observer variability [31]. Detection of acute hypoxia with CPR is the most useful parameter [32].

In this study, we aimed to assess the CPR changes in IO patients, because research seems lacking in this area.

Materials and methods

This prospective case-control study was held in a University hospital between October - November in 2018. After approval of study by the local ethics committee (Kayseri Erciyes University Medical Faculty Ethics Committee, approval ID no: 2018/455), each participant was informed, and consent was obtained. The study population was recruited from 37-40 gestational weeks singleton, isolated oligohydramniotic pregnant women (IO group) based on the last menstrual period and gestational age, gravida, parity, body mass index-matched pregnant women with normal amounts of amniotic fluid volume according to her gestational age (control group). All recruited patients were examined before active labor (cervical dilatation \leq 4cm). Patients who gave birth in three days after the fetal Doppler measurement were included in the study. Fetuses with chromosomal/structural abnormalities and fetal growth restriction, pregnancies with ruptured membranes, multiple gestations, fetal placental, and umbilical cord abnormalities, Rh isoimmunization, patients with maternal systemic disease, pregnancy-induced hypertension, pregestational or gestational diabetes, prior cesarean section, preterm and post-term pregnancies were excluded.

All the participants underwent an ultrasound examination performed by an experienced clinician (E.D.). Obstetric and general health data of each patient were also recorded.

Doppler ultrasound examinations were performed using a Mindray DC-7 ultrasound machine (Shenzhen Mindray Bio-Medical Electronics Co., China), equipped with a 3,5-MHz convex array sector transducer, taking into consideration fetal movements, and breathing periods. After fetal ultrasound examination of fetal middle cerebral artery (MCA), and umbilical artery (UA), pulsatility index, systolic-to-diastolic ratio (S/D), peak systolic velocity (PSV) of MCA were measured and recorded. Amniotic volume was measured with a four-quadrant amniotic fluid index technique and AFI \leq 5 cm was considered oligohydramnios. IO group and control group were compared in terms of fetal CPR and adverse perinatal outcomes.

Statistical analysis

The SPSS for Windows 21.0 (SPSS Inc.IL, USA) software was used for statistical analyses. *P*-value <0.05 was considered statistically significant. The Shapiro-Wilk test was used to assess the normality of distribution of variables. Normally distributed variables were expressed as mean (SD). Comparisons of variables between the groups were performed by independent samples t-test, Mann-Whitney U test, and Chi-square test.

Results

A total of 98 women who met the inclusion criteria were recruited for the study. Comparison of both groups' demographic and fetal Doppler parameters was shown in Tables 1 and 2. The demographic features of both groups were similar, but perinatal

adverse outcomes were significantly higher in the IO group. The mean maternal age of the whole study population was 27.3 (5.9) years. Twenty-seven of 98 pregnant women (27.6%) were on their first pregnancy, while 71 (72.4%) women were on their second or more pregnancy. The average gestational age of inclusion in the study was 38.3 (1.05) weeks according to the last menstrual period (LMP) (Table 1).

Comparison of all Doppler indices showed a statistical difference between the groups (UA PI $P=0.014$, UA S/D $P=0.01$, MCAPI $P=0.004$, MCA PSV $P=0.037$ and CPR $P<0.001$) (Table 2). Patients with low fetal biophysical profiles (BPP ≤ 4) and impaired CPR (CPR <1.08) showed a significant correlation among themselves ($r=0.23$ positive correlation $P=0.02$, Spearman Rho test). The coexistence of low BPP scores and low CPR levels in the IO group resulted in a significant increase in C/S rates due to fetal distress (Table 3). Also, there was a significant correlation between low CPR and fetal distress among the groups ($r=0.035$, $P<0.001$). In patients with low BPP in the IO group, the CPR levels of 7 patients were higher than 1.08, while 8 patients' CPR was <1.08 ($P=0.078$). Statistical results showed significant differences between the groups in terms of 1st and 5th minute APGAR scores and admission to NICU. In both groups, patients with low BPP scores were associated with lower 1st and 5th minute APGAR scores ($r=0.40$ $p<0.001$, $r=0.32$ $P=0.001$ respectively), higher fetal distress ($r=0.34$ $P=0.001$) and C/S rates ($r=0.25$ $P=0.013$) ($P=0.023$). No stillbirth or neonatal deaths were observed in any of the groups.

Table 1: Maternal demographic and obstetric features of the whole study population

Characteristics	Oligohydramnios group n=45	Control group n=53	P-value
Maternal age(year)*	26.4(5.48)	28.1(6.23)	0.15
Gestational age(week)**	37.2(1.9)	37.5(1.8)	0.2
Gravida**	1.98(0.9)	2.24(0.97)	0.15
Parity**	0.82(0.8)	0.87(0.83)	0.81
BMI (kg/m ²)*	27.01(4.7)	27.18(4.4)	0.85
Gender male†	28(62.2%)	25(47.2%)	0.13
Induction and/or augmentation of labor (oxytocin) †	12(26.7%)	17(32.1%)	0.55
Mode of delivery C/S†	20(44.4%)	16(30.2%)	0.14
Fetal distress (emergency C/S)	15(33.3%)	5(9.4%)	0.003
NICU admission rate	12(26.7%)	2(3.8%)	0.001
1-min Apgar score ≤ 7 †	25(55.6%)	4(7.5%)	<0.001
5-min Apgar score ≤ 7 †	6(13.3%)	1(1.9%)	0.028
Birth weight (g)*	3132(307)	3222(373)	0.21
Birth length (cm)	49.2(1.4)	48.9(2.04)	0.4

* Independent Sample t Test, ** Mann-Whitney u test, † Chi -Square test

Table 2: Fetal Doppler indices of the whole study population

Characteristics	Oligohydramnios group n=45	Control group n=53	P-value
Umbilical artery S/D*	2.64(0.61)	2.38(0.37)	0.01
Umbilical artery PI**	0.84(0.17)	0.76(0.13)	0.014
MCA PI*	1.50 (0.39)	1.74(0.44)	0.004
MCA PSV(cm/s)*	69.2(14.2)	63.1(14.6)	0.037
Cerebro Placental Ratio**	1.99(1.6)	2.34(0.70)	<0.001
Amniotic Fluid Index*	36.8(7.17)	101.3(41.2)	<0.001
Biophysical profile ≤ 4 (n, %)	15(33.3%)	7(13.2%)	0.017

S/D: Systole/ Diastole PI: Pulsatility index PSV: Peak systolic velocity CPR: Cerebro-Placental Ratio

Table 3: Relationship between CPR and BPP in oligohydramnios group

Oligohydramnios group	CPR ≤ 1.08	CPR >1.08	P-value
*BPP ≤ 4	8	7	0.078
BPP >4	8	22	
Apgar1st Min. ≤ 7	9	16	0.94
Apgar1st Min. >7	7	13	
Fetal distress (+)	9	6	0.023
Fetal distress (-)	7	23	

* Biophysical profile

Discussion

In this prospective case-control study, we found that patients with low CPR levels were more likely to have a cesarean section (C/S) for non-reassuring fetal heart rates (NRFHR) in the

IO group, and poor perinatal outcomes, such as low 1st and 5th minutes APGAR scores and a higher number of admissions to NICU.

In the literature review, perinatal outcomes of fetuses with IO have conflicting results. A meta-analysis made by Rossi and Prefumo in 2013 showed no significant differences concerning perinatal outcomes, except a rise in C/S rates due to NRFHR [19], which did not lead to an increased low incidence of APGAR scores, low umbilical artery pH, NICU admissions, or mortality compared to pregnancies with normal amniotic fluid. Also, they did not find any increase in meconium-stained amniotic fluid, which is another conflicting issue in oligohydramnios. The other two studies revealed similar results. In one of them, Karahanoglu et al. [33] investigated the optimal timing of delivery for IO patients. They stratified the patients as early term, full-term, and late-term, and analyzed the perinatal outcomes to find no differences in terms of NICU admission, low APGAR score, and low cord pH. However, this study had two limitations, one being its retrospective nature and the other, the lack of a control group. In the second study, which was also retrospectively designed, Naveiro-Fuentes et al. [34] stated that IO was not associated with poor perinatal outcomes, except for fetuses with SGA.

On the other hand, the recent two meta-analyses reported a relationship between IO and poor perinatal outcomes. In 2016, Shrem et al. [25] showed higher C/S rates due to NRFHR, lower 1st, and 5th minute APGAR scores, and more admission to NICU in the IO group compared to pregnancies with normal amniotic fluid, similar to our study. Another meta-analysis was performed by Rabie et al. [24] in 2017, which also reported results parallel to ours: Low APGAR score in 5th minute and higher C/S rates due to NRFHR. They also found an increase in meconium aspiration syndrome which we did not assess. In another study, Casey et al. [8] reported higher stillbirth rates in the IO group. We did not observe any stillbirth, but this may have resulted from a relatively small sample size of the cohort.

In 2017, Khalil et al. [35] demonstrated that low CPR is significantly associated with impaired fetal growth and poor neonatal outcomes, even in appropriate for gestational age (AGA) fetuses. They stated that low CPR is a biometric marker of failure to reach growth potential even in AGA fetuses (\geq the 10th percentile). Also, several studies have been reported a relationship between low CPR and adverse outcomes in low risk and/or AGA pregnancies [36-44]. In 2018, Kalafat and Khalil published a review about the utility of CPR in SGA and AGA fetuses, and they underlined the importance of close intrapartum surveillance of AGA fetuses due to the risk of fetal intrapartum compromise and operative delivery [45].

In the present study, further evaluation of fetal well-being status was also performed with a biophysical profile (BPP). Fetuses with low BPP (BPP ≤ 4) had more C/S rates due to NRFHR and lower 1st and 5th minute APGAR scores. These results were consistent with the literature [46,47]. Moreover, CPR levels were positively correlated with BPP scores. We think that these results may be related to an unrecognized subtle placental insufficiency in IO.

Limitations

Although our study is the first on this subject, several limitations remain. The main limitation of our study is the relatively small size of the cohort. Secondly, we did not assess umbilical cord pH alterations and the existence of meconium-stained amniotic fluid among the groups to evaluate the poor neonatal outcome.

Conclusion

As mentioned above, the perinatal outcomes of IO are controversial in the literature. Our present study showed an increase in C/S rates due to non-reassuring fetal heart rate patterns, lower 1st and 5th minute APGAR scores, and higher NICU admission rates in IO patients with low CPR. Since our study is the first to investigate the relationship between IO and CPR, we recommend clinicians to closely follow up IO patients with low CPR levels and BPP scores due to risk of fetal distress and poor neonatal outcomes.

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