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Comparison of maternal circulating collectrin levels in pregnancies complicated by oligohydramnios and fetal growth restriction

Oligohidramniyos ve fetal büyüme geriliği ile komplike olan gebeliklerde annenin dolaşımındaki collectrin düzeylerinin karşılaştırılması

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ABSTRACT

Aim: Collectrin is a transmembrane regulatory glycoprotein involved in the renin-angiotensin system and plays an important role in kidney development. It is well known that placental perfusion play essential role in maintaining amniotic fluid production and fetal development. The current study sought to assess the relationship between serum collectrin levels and fetal growth restriction (FGR) and oligohydramnios.

Materials and Methods: This observational study was done in a tertiary level maternity hospital. The study groups were comprised of pregnancies complicated with term oligohydramniosis and isolated FGR. The control group was selected from among low risk healthy pregnancies. Demographic features, obstetric characteristics, gestational age, amniotic fluid index, fetal biometric measurements, doppler indices, blood pressure, pulse, hematologic, and biochemical parameters, and serum collectrin levels were recorded for each patient.

Results: No significant differences were observed among the groups with regard to maternal age, body mass index, gesational week, and peripheral blood pressures (p>0.05). The birth weights were statistically significantly lower in the FGR group than the other 2 groups (p<0.001). There were no significant differences in the neonatal outcomes between these groups. Maternal serum hematologic parameters and biochemical markers were similar among the groups with the exception of chloride. Collectrin values were 129.8±187.7, 120.8±52.8, and 116.7±33.5 ng/ml in the controls, FGR and oligohydramnios groups, respectively (p:0.003).

Conclusion: Maternal circulating collectrin levels is lower in pregnancies complicated with oligohydramnios and FGR than in the low risk term pregnacies. Collectrin may be a valuable biomarker for diagnosing oligohydramnios and FGR which are characterized by placental hypoperfusion.

Keywords: Collectrin, fetal growth retardation, oligohydramnios, renin–angiotensin system, placenta

ÖZ

Amaç: Collectrin, renin-anjiyotensin sisteminde yer alan transmembran düzenleyici bir glikoproteindir ve böbrek gelişiminde önemli rol oynar. Plasental perfüzyonun amniyotik sıvı üretiminin ve fetal gelişimin sürdürülmesinde önemli rol oynadığı iyi bilinmektedir. Mevcut çalışma serum collectrin düzeyleri ile fetal büyüme geriliği (FBG) ve oligohidramniyoz arasındaki ilişkiyi değerlendirmeyi amaçladı.

Gereç ve Yöntemler: Bu gözlemsel çalışma üçüncü basamak bir doğum hastanesinde yapıldı. Çalışma grupları term oligohidramniyoz ve izole FBG ile komplike olan gebeliklerden oluşturuldu. Kontrol grubu ise düşük riskli sağlıklı gebelikler arasından seçildi. Her hastanın demografik özellikleri, obstetrik özellikleri, gebelik yaşı, amniyotik sıvı indeksi, fetal biyometrik ölçümler, doppler indeksleri, kan basıncı, nabız, hematolojik ve biyokimyasal parametreler ve serum collectrin düzeyleri kaydedildi.

Bulgular: Anne yaşı, vücut kitle indeksi, gebelik haftası ve periferik kan basıncı açısından gruplar arasında anlamlı farklılık gözlenmedi (p>0,05). FBG grubunda doğum ağırlıkları diğer 2 gruba göre istatistiksel olarak anlamlı derecede düşüktü (p<0,001). Bu gruplar arasında neonatal sonuçlar açısından anlamlı bir fark yoktu. Maternal serum hematolojik parametreleri ve biyokimyasal belirteçler klorür haricinde gruplar arasında benzerdi. Collectrin değerleri kontrol, FBG ve oligohidramnios gruplarında sırasıyla 129,8±187,7, 120,8±52,8 ve 116,7±33,5 ng/ml idi (p:0,003).

Sonuç: Oligohidramniyoz ve FBG ile komplike olan gebeliklerde, annenin dolaşımdaki collectrin düzeyleri düşük riskli term gebeliklere göre daha düşüktür. Collectrin, plasental hipoperfüzyon ile karakterize olan oligohidramniyoz ve FBG'nin teşhisinde değerli bir biyobelirteç olabilir.

Anahtar Kelimeler: Collectrin, fetal büyüme geriliği, oligohidramnios, renin-anjiyotensin sistemi, plasenta

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INTRODUCTION

Oligohydramnios is defined as diminished amniotic fluid volume (AFV) according to the gestational age. It was shown that reduced AFV is generally associated with poor fetal and neonatal outcomes (1). A physiological change in AFV is seen during the course of pregnancy. It gradually increases until the 36th week of pregnancy, afterwards it remains stable. Beyond the 40th gestational week, AFV tend to be decreased and oligohydramnios is frequently seen in postterm pregnancies. Many diseases or factors belong to the mother, placenta or fetus can cause this condition (2). However, the etiological factors cannot be defined in the half of the oligohydramnios cases and they are diagnosed during the last part of the pregnancy (3). Fetal growth restriction (FGR), on the other hand, is used to describe fetuses with an estimated fetal weight below a certain threshold for gestational age, most commonly under the 10th percentile or 2 SD according to growth curve (4, 5). The prevalence of FGR ranges between 0.5 % -5 %. It is commonly related with increased perinatal morbidity and mortality due to fetal distress, low Apgar score, and meconium aspiration syndrome, which are consequences of placental insufficiency (6, 7). It has also various etiological reasons. As in the oligohydramnios, the etiological factors cannot be defined in many of the cases and called as idiopathic FGR. It is believed that the underlying reason for this is placental insufficiency, which is pathophysiologically characterized by impaired placental development, incomplete decidual invasion of the cytotrophoblasts, and distortion of spiral arteries (7).

From the 6th week of pregnancy, the Renin-angiotensin system (RAS) is present in the fetal circulation and regulates blood pressure and fluid volume. All components of the RAS are located in the placenta. Circulating RAS is closely associated with villous and extravillous cytotrophoblast proliferation, extravillous cytotrophoblast invasion, cell migration and placental angiogenesis (89. Collectrin is a glycoprotein in the kidney's collecting system and functions in the RAS. It is structurally similar to angiotensin converting enzyme-2 (ACE-2). It has been shown that kidney superoxide radicals increase and nitric oxide (NO) decrease, resulting in impaired vasodilatation in collectrin knockout mice. NO is synthesized by an enzyme called endothelial NO synthase (eNOS) which is located in the vascular endtotelium. NO–eNOS formation is essential for the vascular tonus and regulates blood pressure. In the absence of collectrin, it has been observed that eNOS formation is impaired, causing hypertension (9, 10). In this study, we hypothesized that decreased collectrin levels might cause placental hypoperfusion, leading to oligohydramnios and FGR. We aimed to measure serum collectrin concentrations in oligohydramnios, FGR and low-risk term pregnancies and compare them with each other.

MATERIALS AND METHODS

Our study was planned as an observational cross-sectional study. It was performed on 125 consecutive pregnant women who applied to our hospital for pregnancy control between January and June 2021 and met the inclusion criteria. Our hospital is a state-supported 3rd level hospital and is placed in the capital city of Turkey, Ankara. All pregnant women included in the study had a confirmed pregnancy of 37 weeks and above. The patients were selected from women aged 18-44 years. Labor induction was decided for those diagnosed with oligohydramnios and FGR. Study groups consisted of isolated term oligohydramnios (group 1, n:40), idiopathic FGR (group 2, n:40) and low risk term pregnants (group 3, n:45). Exclusion criteria for the study groups were as follows; any systemic diseases such as hypertension, diabetes, renal disease, pathological obstetric conditions such as preeclampsia, preterm labor, multiple pregnancy, rupture of membranes, fetal anomalies, and placental abnormalities. AFV was determined using the amniotic fluid index (AFI) or deepest vertical pocket (DVP). A DVP value lower than 2 cm was considered as oligohydramnios. Alternatively, the abdomen was divided into four quadrants at the navel level to measure DVP in each quadrant. AFI, representing the sum of four DVPs less than 5 cm, was used to diagnose oligohydramnios (11). Fetal weight was estimated using four biometric measurements: abdominal circumference, femoral length, biparietal diameter, head circumference. Each measurement was repeated three times; the mean measurement was considered for the estimation of fetal weight according to the Hadlock method. The diagnosis of FGR was made when it was below the 10th percentile (12). The same experienced clinician performed the ultrasound scans. Each patient's blood

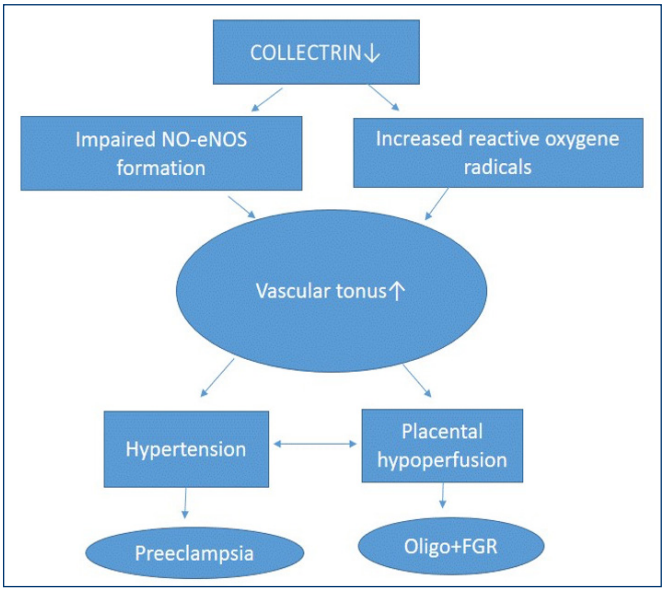

Figure 1. It shows the conditions that may develop due to changes in vascular structures in case of a decrease in collectrin level.

pressure and other vital signs were also recorded. Before active labor or labor induction, fasting venous blood samples were taken for routine tests and collectrin measurement. Blood sample for collectrin measurement was collected in an anticoagulant-free biochemistry tube, and were centrifuged for 15 seconds at 1,000 g. The serums were separated and frozen at -80 C until the working day. An enzyme-linked immunosorbent assay (ELISA) was used to determine serum colletrin levels (Human TMEM27 ELISA kit, Elabscience, catalog No. E-ELH5400, Bethesda, MD, USA). Manufacturer's instructions were followed. In the last step of the procedure, absorbance values were measured at 450 nm in a microplate reader. After drawing a standard curve from the measured absorbances against known concentrations, the collectrin levels were expressed in ng/ml. A written and verbal informed consent were taken from the all participants before the study enrollment. Institutional ethic committee approved by the study protocol (date/decision no: E2-21-455).

All data analyzes were calculated by using the SPSS software version 22.0 (Chicago, IL, USA). The normal distribution of the each variable was tested with Kolmogorov-Smirnov test. Data were presented as mean (SD) , median (range), numbaer (percentage). Comprisons of the variables among the groups were done by Kruskal wallis test, one way ANOVA with post-hoc Tukey's b test or chi sqaure test where appropraite. A P Value≤0.05 was considered statitstically significant.

RESULTS

A total of 125 pregnant women, 40 in the first two groups and 45 in the control group, were included into the study. There was no statistically significant difference in the mean maternal ages, weeks of gestation and body mass indexes in the groups (p>0.05). Gravidity, parity, number of previous misscarriges were similar. Weigh gain in pregnancy were statistically insignificant between the groups, but it is lowest in Group 2 and when compared Group 3 statistically remarkably lower (p:0.046). Number of pregnant women who smoked were comparable among the groups (p:0,272). While the mean blood pressures were similarly distributed between the groups, the values were measured within normal limits in each patient (Table 1).

Table 1. Comparison of clinical and demographic features of the groups.

GROUPS VARIABLES	Group 1 Oligohydramnios (n:40)	Group 2 FGR (n:40)	Group 3 Control (n:45)	P-value	pI-II	pI-III	pII-III
Age, (years)	26.5±5.1	26.1±5.4	26.9±5.6	0.236	0.735	0.443	0.270
Gravidity	2(1-5)	2(1-5)	2(1-5)	0.449	0.825	0.398	0.552
Parity	0(0-3)	0(0-3)	1(0-3)	0.218	0.731	0.196	0.186
Abortion	0(0-3)	0(0-2)	0(0-2)	0.667	0.532	0.593	0.896
Gestational age, (weeks)	39.2±1.0	38.8±1.2	39.4±1.0	0.110	0.095	0.742	0.067
BMI, (kg/m²)	29.8±4.6	28.5±5.2	29.5±4.9	0.720	0.564	0.880	0.876
Co-morbidity, n(%) **Hypothyroidism** **Asthma** **Arythmia**	 3(8.6) 0 1(2.9)	 3(8.6) 1(2.9) 0	 4(10) 0 0	0.479	0.428	0.334	0.456
GWG (kg)	12.9±5.4	11.2±4.6	14.1±5.3	0.059	0.356	0.589	0.046
AFI (total) (cm)	4.2±0.8	4.0±0.6	10.1±2.2	<0.001	0.668	<0.001	<0.001
Smoking, n(%)	2(5)	3(7.5)	5(11.1)	0.372	0.493	0.116	0.280
SBP (mmHg)	118.2±9.7	118.9±9.5	119.5±7.9	0.887	0.676	0.700	0.831
DBP (mmHg)	70.1±7.8	72.7±7.9	70.8±6.5	0.242	0.160	0.745	0.134
Pulse (/min)	87.7±8.5	88.7±7.9	90.1±8.1	0.480	0.864	0.272	0.340
Route of birth, n(%) **NVB** **C-Birth**	 28(70) 12(30)	 29(72.5) 11(27.5)	 27(60) 18(40)	0.588	0.982	0.269	0.216

BMI: body mass index, GWG: gestational weight gain, SBP: systolic blood pressure, DBP: diastolic blood pressure, NVB:normal vaginal birth, C-Birth: cesarean birth. Data were presented as mean±standard deviation (SD), median (range), number (percentage). A p value<0.05 was considered as statistically significant.

Table 2. Laboratory parameters and neonatal outcomes of the patients.

GROUPS VARIABLES	Group 1 Oligohydramnios (n:40)	Group 2 FGR (n:40)	Group 3 Control (n:45)	P-value	pI-II	pI-III	pII-III
Birth weight (gr)	3380±350	2750±255	3360±290	0.000	0.000	0.880	0.000
Birth height (cm)	50.5±1.5	48.5±1.4	50.2±1.5	0.000	0.000	0.912	0.000
Fetal gender, n(%) **Girl** **Boy**	 19(47.5) 21(52.5)	 23(57.5) 17(42.5)	 25(55.5) 20(45.5)	0.560	0.492	0.378	0.890
Apgar 1.'	7(5-7)	7(4-7)	7(6-7)	0.722	0.476	0.905	0.233
Apgar 5.'	9(8-9)	9(5-9)	9(8-9)	0.494	0.430	0.798	0.274
NICU admission, n(%)	3(7.5)	4(10)	2(4.4)	0.335	0.587	0.454	0.210
Glucose , (mg/dl)	82.1±9.8	80.5±9.7	78.7±8.8	0.300	0.749	0.269	0.699
Blood urea nitrogen, (mg/dl)	17.7±4.1	17.5±4.6	16.8±4.6	0.588	0.981	0.599	0.721
Creatinine , (mg/dl)	0.5±0.1	0.5±0.1	0.5±0.1	0.375	0.877	0.354	0.656
Total protein, (mg/dl)	67.1±4.0	65.1±4.7	66.9±4.5	0.137	0.172	0.983	0.214
Albumine, (mg/dl)	40.1±2.9	39.4±3.7	40.4±4.2	0.193	0.175	0.795	0.449
Aspartate transaminase, (U/L)	17.4±5.2	17.7±5.4	17.4±5.6	0.957	0.968	1.000	0.960
Alanine transaminase, (U/L)	15.5±9.4	15.4±6.9	14.9±7.1	0.938	0.999	0.945	0.955
Total bilirubin, (mg/dl)	0.5±0.2	0.5±0.2	0.6±0.2	0.654	0.972	0.794	0.651
Direct bilirubin, (mg/dl)	0.1±0.05	0.1±0.06	0.1±0.07	0.821	1.000	0.853	0.853
Sodium, (mEq/L)	137.5±2.1	137.3±1.8	137.3±1.9	0.767	0.812	0.792	1.000
Potassium, (mEq/L)	4.0±0.3	4.1±0.3	4.0±0.2	0.098	0.202	0.964	0.109
Clorid, (mEq/L)	106.3±2.2	105.0±2.3	105.9±1.6	0.029	0.026	0.698	0.140
Protrombin time, (sec.)	11.9±0.6	11.7±0.8	11.6±0.7	0.167	0.386	0.156	0.874
INR	1.02±0.06	0.99±0.05	0.98±0.06	0.049	0.151	0.050	0.901
aPTT, (sec.)	24.4±1.9	24.3±1.7	24.2±2.2	0.958	0.995	0.956	0.980
Fibrinogen, (mg/dl)	369.2±61.9	394.7±39.1	376.9±32.1	0.060	0.054	0.743	0.216
White blood cell, (10^9/L)	9.2±2.1	9.4±2.3	9.0±2.4	0.805	0.958	0.929	0.789
Hemoglobin, (g/dl)	12.2±1.4	12.0±1.4	11.7±1.1	0,364	0.786	0.331	0.739
Hematocrit, (%)	36.9±3.5	36.2±4.2	35.2±3.0	0.155	0.700	0.134	0.514
Platelet, (x10^3/mcL)	254.3±57.7	272.9±64.0	251.1±59.0	0.254	0.401	0.972	0.264
Collectrin, (ng/ml)	116.7±33.5	120.8±52.8	129.8±187.7	0.003	0.385	0.000	0.039

NICU:neonatal intensive care unit, INR: international normalized ratio, aPTT: activated partial thromboplastin time. Data were presented as mean±standard deviation (SD), median (range), number (percentage). A p value<0.05 was considered as statistically significant.

No significant difference were obseved between the groups in terms of delivery type and baby's gender (all $p > 0.05$). Birth weight was lower in Group 2 compared to Groups 1 and 3 as expected ($p < 0.001$). However, there was no significant difference between Apgar scores and NICU acceptance rates.

Comparison of hematological and biochemical parameters is shown in Table 2. Serum chloride levels were 106.3 ± 2.2 mmol/L in Group 1, 105.0 ± 2.3 mmol/L in Group 2, and 105.9 ± 1.6 mmol/L in Group 3 (p:0.020). Maternal serum collectrin values were 116.7 ± 33.5 ng/mL in oligphydrmnios group, 120.8 ± 52.8 ng/ml in FGR group and 129.8 ± 187.7 in control group (p:0.003). When pairwise comparisons were made between the groups, it was found that Group 1 and 2 were lower than Group 3 (both $p < 0.05$) and similar between Group 1 and Group 2 (p:385).

DISCUSSION

The current study sought to assess the relationship between maternal serum collectrin levels and FGR and oligohydramnios. Collectrin plays an essential role in regulating blood pressure. Oligohydramnios and FGR are the two common obstetric conditions, mainly due to placental vascular impairment. We found that the maternal serum collectrin level is significantly lower in pregnancies complicated with oligohydramnios and FGR than in low risk pregnancies.

AFV is the result of the balance between fluid production and absorption in the gestational sac. In the first half of pregnancy, lung secretions, maternal plasma transition throughout the fetal membranes, and fetal urine make up most of the amniotic fluid

production. After the 16th week of gestation, fetal kidneys begin urine production, and fetal urine comprises the vast majority of AFV until delivery (13). Therefore, the anomalies in the fetal genitourinary system that result in oligohydramnios are usually diagnosed from the 16th to the 18th week of gestation. There are three (maternal-fetal and placental) leading causes of oligohydramnios. Oligohydramnios due to maternal causes is usually associated with some systemic diseases or obstetric conditions that cause uteroplacental insufficiency. Possible causes include particularly vascular disease such as hypertension, preeclampsia, diabetes, and substance abuse, some drugs, and hereditary or acquired thrombophilias (14). Among the fetal causes, the most common cause is premature rupture of amniotic membranes. Fetal genitourinary abnormalities are also associated with oligohydramnios. Post-term pregnancies, FGR, chromosomal abnormalities, and fetal demise are other causes of oligohydramnios (14). Placental pathologies, including placental detachment and twin transfusion syndrome, comprise the minority of cases. Idiopathic oligohydramnios is, particularly in the last trimester, the most common (higher than 50% of cases) form of oligohydramniosis and typically has a favorable obstetric outcome. There is very little data evaluating the relationship between oligohydramnios and placental histology. Acute and occult placental hypoperfusion may be an underlying reason for idiopathic oligohydramnios. In our study, compatible with the literature, idiopathic cases were diagnosed at term, and most had better neonatal outcomes. We also diagnosed oligohydramnios using MVP and AFI measurements (15).

The diagnosis of FGR is made according to an estimated fetal weight below -2 SD or below the 10th percentile on the growth curve. On the other hand, small for gestational age (SGA) is considered as birth weight under the 10th percentile for babies born at that gestational age. These two terms cannot fully correspond to each other. FGR also known as intra uterine growth restricted fetus means growth abnormality (slowing and stopping of fetal growth with or without abnormal Doppler measurements) or being a change in fetal measurement rates in follow-ups during the course of pregnancy (at least two measurements with three weeks apart) (15). Rarely, they may correspond with inadequate growth, with a weight near the 10th percentile without being SGA. Different cut-off values have been identified for the definition of FGR, such as the 10th, 5th, and 3rd percentiles. However, the severity of FGR increases when lower threshold values are used. Idiopathic FGR cases may be a mild form of the spectrum. In this study, we used the 10th percentile, and all cases were between the 5th and 10th percentiles (15).

Collectrin was first identified in the kidney as a collecting duct-specific transmembrane glycoprotein (9). It is expressed mainly in the kidneys, with the highest levels in the collecting ducts and proximal tubules. There was a 47.8% structural similarity between collectrin and ACE-2. Although collectrin has high molecular similarity with ACE-2, it does not contain any catalytic activity. Disturbances in the expression of enzymes that process angiotensin (Ang) have been observed in the placentas of pregnant women with idiopathic FGR. This causes the imbalance between the vasoconstrictor and vasorelaxant branches of the placental RAS system to be disrupted and Ang-2, which is known to have a vasoconstrictor effect, becomes dominant. Ang-(1-7) has a vasodilator effect and the opposite effect of Ang-2's vasoconstrictor effect. These two factors are associated with FGR, which occurs with the disruption of uteroplacental perfusion [9]. Placental RAS is significant in the development of the functions of the placenta. Placental RAS may also be effective in the deterioration of uteroplacental perfusion in idiopathic fetal developmental retardation (4). ACE-2 is localized in placental syncytial layer, and in case of its disruption, umbilical blood flow and placental perfusion are impaired in the FGR that occurs.[9] In FGR pregnancies, it has been observed that there is a decrease in AFV due to placental disruption.[10] Collectrin and ACE-2 are homologous molecules, but the effects of Collectrin were found to be independent of RAS (10). Collectrin adjusts vascular tonus through NO produced by eNOS; in the absence of collectrin, hypertension occurs.[9] It has been shown that endothelium-dependent vasodilation is impaired as a result of the production of less NO and more superoxide radicals in the kidneys of collectrin knock-out mice (10). L-Arginine is an essential amino acid for NO synthesis and is transported into the cell by collectrin. It has been shown that L-arginine uptake is reduced in endothelial cells of collectrin knockout mice. These findings suggest that the collectrin provides a balance between NO and superoxide by assisting the uptake of L-arginine for NO synthesis, thus having a protective role against endothelium-dependent vasoconstriction and hypertension. Çetin et al. demonstrated that serum collectrin concentrations were significantly lower in pre-eclamptic patients than in control patients, even if they found lower levels in early- onset preeclampsia than in late-onset preeclampsia (16). Similarly, a recent study conducted on pre-eclamptic women also demonstrated that collectrin was lower in early-onset preeclampsia than in late-onset preeclampsia and healthy controls. They found a significant inverse correlation between serum collectrin levels and blood pressure (17). We excluded hypertensive and pre-eclamptic patients, and all women included in the study had blood pressure within normal ranges. Therefore, we could not demonstrate such a relationship between collectrin and blood pressure.

The primary weakness of our study is the scarce of sample size. The cross sectional nature of the study design does not imply a cause-effect relationship. The lack of knowledge about placental

expression of collectrin levels, which would likely provide more accurate data, also limited the study hypothesis. However, our results collectively demonstrated a novel molecular biomarker that contributes to the physiopathology of idiopathic oligohydramnios and FGR. These findings may lead to new diagnostic and therapeutic insights into these two obstetric entities.

In brief, maternal circulating collectrin levels were significantly lower in pregnancies diagnosed with oligohydramnios and FGR. Collectrin may be a valuable biomarker for diagnosing oligohydramnios and FGR characterized by placental hypoperfusion. Our results should be supplemented with further molecular and immunohistochemical studies, including more cases, to reveal the precise relationships between collectrin, oligohydramnios, and FGR.

Institutional Review Board Statement
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the Ankara Cİty Hospital (E2-21-455).

Author Contributions
Conceptualization, M.C. and S.Y.; Methodology, M.C.; S.Y.; E.M.K.; Software, N.H.; Validation, M.C., S.Y. and N.H.; Formal Analysis, T.C. and A.T.; Investigation, M.C.; S.Y.; N.H.; Resources, M.C and N.H.; Data Curation, A.T.; Writing – Original Draft Preparation, N.H.; Writing – Review & Editing, A.T.; Visualization, N.H. and A.T.; Supervision, A.T.; Project Administration, N.H.

Informed Consent Statement
Written informed consent has been obtained from the patients to publish this paper.

Conflicts of Interest
The authors declare no conflict of interest.

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