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**Original research articles** base on clinical or experimental studies. The main text should not exceed 2500 words (max. 16 pages) and there should be a maximum 6 authors

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**Page 3** and next - Main text
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This page should only include the title of the manuscript, which should be carefully chosen to better reflect the contents of the study. No anusual abbreviations should be used in the title of the manuscript. A short title as running heading not exceeding 40 characters should be given which is desired to appear on top part of continuing pages when journal is published.

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References used in the text should be directly related to the topic, as recent as possible and in enough numbers. They should be numbered in square brackets in the order in which they are mentioned in the text including Tables and Figures. Citation order should be checked carefully.

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— ***Book:*** Jones KL. Practical perinatology. New York: Springer; 1990. p. 112-9.

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Each table should be prepared on a separate page with table heading on top of the table. Table heading should be added to the main text file on a separate page when a table is submitted as a supplementary file.

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For a swift peer review, Perinatal Journal operates a web-based submission, peer review and manuscript tracking system. Authors are required to submit their articles online. Details of how to submit online can be found at www.perinataljournal.com.

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# Contents

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# Evaluation of the Results of Cordocentesis: 9 Years of Experience

Turgay Şener[1], H. Mete Tanır[1], Emel Özalp[1], Emre Uysal[1], Beyhan Durak[2], Oguz Çilingir[2], Güney Bademci[2], Sevilhan Artan[2]

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**Abstract**

**Objective:** To evaluate of results of cordosentesis in an University Clinic.

**Methods:** Adequate amount of cord blood was taken from 96.9% of the cases, the successful culture rate was 99.2%. In seven cases the procedure was repeated as the culture was unsuccessful in two of them and maternal contamination was observed in five of them. There was no fetal loss among the 251 cordocentesis cases, but it must be taken into account that 62.2% of these patients were referred to our clinic so that their pregnancy outcomes could not be obtained. The most common complications were intraamniotic bleeding in 6.8% and transient fetal bradycardia in 6.3% of the cases. According to cytogenetic evaluation reports, chromosomal abnormality was detected in 13 cases (5.17%). One case with short femur had a karyotype of 47,XX,t(8;14)(p22;q21),+der(14)(8;14) and one case with single umblical artery having a karyotype of 46,XX,del(3)(p25pter) was described for the first time in the literature.

**Results:** Data including the indications, cytogenetic results and complications was obtained from 251 pregnancies who underwent cordocentesis in a University clinic.

**Conclusion:** Cordocentesis is an invasive prenatal diagnostic and therapeutic procedure with high accuracy and safety if it is carried out by highly skilled physicians and when optimal culture conditions are provided.

**Keywords:** Cordocentesis, pregnancy, prenatal diagnosis, chromosomal aberrations, fetal blood.

## *Dokuz yıllık kordosentez sonuçlarımız*

**Amaç:** Bir üniversite kliniğindeki kordosentez sonuçlarının değerlendirilmesi.

**Yöntem:** İkiyüzellibir gebe kadında yapılan kordosentez sonucunda elde edilen veriler, kordosentez endikasyonları, sitogenetik sonuçları değerlendirildi.

**Bulgular:** Olguların %96.9`undan yeterli kan alınabildi. Kültür başarısı %99.2 oldu. İki olguda kültür başarısız olduğundan, 5 olguda maternal kontaminasyon saptandığından girişim tekrarlandı. Toplam 251 girişim sonrasında fetal kayıp olmadı, ancak olguların %62.2 si dışarıdan refere edilmiş olduğundan gebelik prognozları hakkında net bilgiye ulaşılamadı. En sık karşılaşılan komplikasyonlar olguların %6.8`inde intraamniotik kanama, %6.3'ünde geçici fetal bradikardi idi. Sitogenetik değerlendirmeye göre anormal kromozomal sonuçlar 13 olguda (%5.1) saptandı. Femur kısalığı olan bir olguda literatürde ilk kez tanımlanan 47,XX,t(8;14)(p22;q21),+der(14)(8;14); tek umbilikal arteri olan bir olguda 46,XX,del(3)(p25pter) sonucu elde edildi.

**Sonuç:** Kordosentez, bu konuda yetenekli hekimlerce yapıldığında ve uygun laboratuar kültür koşulları sağlandığında yüksek güvenirliği olan invaziv bir tanısal ve tedavisel girişimdir.

**Anahtar Sözcükler:** Kordosentez, gebelik, prenatal tanı, kromozom aberasyonları, fetal kan.

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## Introduction

Cordocentesis is an interventional prenatal diagnosis and treatment method which can be applied from 14th gestational week up to term and enables early diagnosis of various intrauterine genetic, infectious, metabolic and hematologic diseases at prenatal period and treatment at appropriate cases.[1] However, mortality is often at practices before 16th week.

It can be used in diagnosis of genetic hematologic and metabolic diseases and in cases where chromosomal structure of fetus is determined rapidly when family applies lately, prenatal diagnosis methods applied previously are ineffective or give suspicious results, fetal anomaly is detected in ultrasonography. Evaluation of fetal metabolic situation in intrauterine growth retardation (IUGR), diagnosis of intrauterine infections, evaluation and treatment of fetus in immune hydrops and auto-immune thrombocytopenic pregnants are the other cordocentesis indications.[2,3]

Chorioamnionitis, maternal complications and fetal loss like adult-type respiratory distress syndrome, intraamniotic bleeding, fetal bradycardia, umbilical cord hematoma and thrombosis, and fetal complications such as premature membrane rupture, premature delivery and feto maternal transfusion may be seen in cordocentesis interventions.[4]

Some factors such as experience of physician performing cordocentesis practice, ultrasonogprahic image quality, gestational week, maternal cooperation, maternal obesity, amnion fluid volume, fetus position, fetal mobility, placenta location, targeted umbilical cord piece and needle diameter have a direct effect on initiative success.[5]

## Methods

Two hundred and fifty-one cordocentesis cases analyzed for chromosome at Medical Genetic Department and applied for prenatal diagnosis in the Department of Obstetrics and Gynaecology, Medicine Faculty, Eskişehir Osmangazi University in between 2000 and 2008 were evaluated retrospectively for initiative indications, cell culture success, detected chromosomal anomalies and genetic results.

All cases were informed in detail about the initiative and possible complications before the cordocentesis initiative and informed consent forms were taken. Their previous pregnancies and prognoses were questioned and registered into the form. Age, gravida, parity, abourtus and living children number, gestational week and blood groups of cases were noted down. The existence and degree of kinship between spouses and the history of baby with anomaly within the family were researched. History of chromosomal inherited diseases was questioned and pedigree analysis and general physical examination was performed on each patient. All fetuses were scanned by ultrasonography for anomalies and placental localization was recorded.

Cordocentesis indications of pregnants were the fetal anomaly in USG, high risk at triple scanning test (1/270 and above), advanced maternal age (≥35), advanced genetic analysis (amniocentesis and CVS confirmation, mosaic karyotype, amniocentesis culture failure), hydrops fetalis, intrauterine growth retardation, negative obstetric history, baby with anomaly history and intrauterine infection suspicion.

Toshiba Sonolayer SSA-250A USG device was used in the initiatives. Sterile gauze bandage, 2 pcs. 5 ml and 2 pcs. 2 ml sterile injectors, spinal needle and heparine to be used during the cordocentesis process were prepared before the initiative. Cordocentesis initiatives were performed by 2 operators by free hand technique between 15th and 38th gestational weeks. Before the cordocentesis process, abdominal region of patient was disinfected by 10% povidion iodine solution and other open regions were covered with sterile cover. Sedation, anesthesia, antibiotics, tocolytic was not applied to any case before and after initiative. 20 cm 22 G spinal needle and injectors

washed with heparin for blood samples were used on all cases. Before initiating the process, positions of fetus and umbilical cord, localization of placenta and fetal heart rate were determined by ultrasonography.

Placental insertion or free piece of cord was aimed as the initiative location. Cordocentesis was performed through cord insertion spot by passing as transplacentally in appropriate cases depending on the location of placenta, or through free cord by passing transamniotically or by entering umbilical vein 1-2 cm away from the insertion point from cord to placenta and 1-5 ml blood sample was taken into injector with heparin. After cord blood was taken, spinal needle was rotated parallel to its shaft and removed from abdominal wall and the process was ended. Then fetal viability was established by ultrasonography. The region (placental or free cord) where initiative was performed on each case, the success of initiative, blood sample volume and Rh incompatibility were recorded. The blood volume taken was varying according to gestational age and indication. Complications during the process, unsuccessful initiative, bleeding into amniotic fluid and fetal bradycardia were also indicated.

Anti-D Immunoglobulin (300 mcgr) was applied to all Rh (-) patients after initiative. All cases after the process were checked at least once by USG in terms of fetal heart rate and possible complications. After samples were taken, they were immediately delivered to the cytogenetic division of Medical Genetic Department. Maternal contamination possibility was eliminated by Apt test (hemoglobin alkaline denaturation test).[6,7] 72 hours of lymphocyte culture was prepared within ready to use media by using fetal blood lymphocytes induced by phytohemagglutinin (PHA). Metaphase solutions prepared by cultures treated with 0.1 μg/ml (10 μg/ml) colsemid for 45 minutes at the end of the duration were stained by GTG and C banding techniques and were taken into microscopic examination. At least 25 metaphase plates of each case were examined, metaphase and karyotype images of cases were detailed in image analysis system (Applied Imaging CytoVision) and they were archived. Cases detected numeric/structural chromosomal anomalies were evaluated in perinatology council and required genetic consultation was provided to families and they were informed accordingly.

SPSS software, student's t-test and Fischer exact x2 test were used for statistical studies. In the statistical evaluation, $p<0.05$ was deemed as significant.

## Results

Cordocentesis initiative was tried on 259 cases in between 15th and 33rd gestational weeks taken into our studies. The initiative failed on 8 cases due to technical reasons and cordocentesis material was taken from totally 251 cases. While 161 of these 251 cases (64.1%) were referred to our clinic, 90 of 251 cases (35.9%) were followed in our clinic. The cordocentesis process was repeated totally in 7 cases since maternal bleeding occurred in 5 cases and there was no reproduction in the culture in 2 cases. Mean age of pregnants was 37.7±2.39 (34-42). Mean pregnancy of cases was 2.57±1.64, mean abortus was 0.74±1.21 and mean living child was 1.0±0.89. Mean gestational week of pregnants who has cordocentesis initiative was 23.4±3.56. Among cordocentesis indications, fetal anomaly at USG was 37.8%, high risk at triple scanning test was 25.5% and advanced maternal age was 10.8%. Mean age of cases with advanced maternal age indication was 37.7±2.39 (34-42). Cordocentesis indications and distributions are given in Table 1.

The most frequently observed anomalies in 98 cases (39%) with fetal anomaly detected by USG were single umbilical artery (20.4%), ventriculomegaly (16.3%) and hydronephrosis (11.2%). The distribution of anomalies is given Table 2.

While placental insertion point of umbilical cord was used as the insertion point of spinal

**Table 1.** The distribution of cordocentesis indications.

| Cordocentesis indication | Cases | Cases with chromosomal anomaly* | Chromosomal anomaly |
|---|---|---|---|
| Fetal anomaly at USG | 98 | 6 | 6.1% |
| High risk at triple scanning test | 66 | 1 | 1.5% |
| Advanced maternal age | 28 | 4 | 14.2% |
| Advanced genetic analysis** | 13 | 1 | 7.6% |
| Hydrops fetalis | 15 | – | – |
| IUGR*** | 14 | – | – |
| Bad obstetric history | 7 | 1 | 14.2% |
| Baby history with anomaly | 7 | – | – |
| Intrauterine infection | 3 | – | – |
| Total | 251 | 13 | 5.7% |

***** *Percent calculations are done within groups.*

****** *Amniocentesis, CVS confirmation, suspicious (mosaic) karyotype, amniocentesis culture failure.*

******* *Intrauterine growth retardation.*

needle in 177 of cases (70.5%), sampling was done through the free part of umbilical cord in 74 cases (29.5%). Placenta was anterior located in 65.7% of cases, posterior located in 25.2% of cases, fundal located in 5.1% of cases, right lateral located in 2.4% of cases and left lateral located in 1.6% of cases. No statistical correlation was found between the insertion point of spinal needle and the success of the process ($p>0.05$). Mean blood sample volume taken from the cases was 4.30±2.17 ml. Prophylactic Anti D Ig (300mcgr) was administrated to 10.8% of cases due to Rh incompatibility. Limited amount of intraamniotic bleeding was observed in 17 of 251 cordocentesis initiatives (6.8%) after the process. All these bleedings took only 2 minutes or less and they stopped spontaneously. Bradycardia developed after the process in 16 of cases (6.3%). Statistically no significant difference was observed between cases with bleeding and without bleeding in terms of bradycardia development after bleeding ($p>0.05$). Blood could not be taken from 8 cases due to technical issues and placenta was posterior located in 5 of them and anterior located in 3 of them.

**Table 2.** The distribution of ultrasonographic anomalies detected in cordocentesis cases.

| USG anomaly finding | Cases |
|---|---|
| Single artery, single vein | 20 |
| Ventriculomegaly | 16 |
| Hydronephrosis | 11 |
| Choroid plexus cyst | 7 |
| Multiple congenital anomaly | 6 |
| Hypoplastic left heart | 5 |
| Echogenic focus at heart | 4 |
| Cystic hygroma | 4 |
| Extremity anomaly | 4 |
| Renal dysplasia | 3 |
| Orofacial defect | 3 |
| Hydrocephaly | 3 |
| Anencephaly | 2 |
| Diaphragmatic hernia | 2 |
| Other minor anomalies | 8 |

Chromosomal anomaly was detected in 13 cases (5.2%) after genetic evaluation of cordocentesis cases. The distribution of these cases is given in the Table 3.

## Discussion

Cordocentesis is a prenatal diagnosis and treatment method which can be applied on 2nd and 3rd trimesters of pregnancy. While it is

**Table 3.** The relationship between chromosomal anomalies detected in cordocentesis cases and age, gestational week, and cordocentesis indication.

| No | Chromosomal anomaly | Comment | Age | Gestational week | Cordocentesis indication |
|---|---|---|---|---|---|
| 1 | 47, XY, +21 | Classical Down Syndrome | 37 | 20 | Advanced maternal age |
| 2 | 47, XY, +21 | Classical Down Syndrome | 29 | 23 | Abnormal USG |
| 3 | 47, XY, +21 | Classical Down Syndrome | 36 | 22 | Advanced maternal age |
| 4 | 47, XY, +13 | Trisomia 13 | 34 | 21 | Abnormal USG |
| 5 | 47,XX,t(8;14)(p22;q21), +der(14)(8;14) | Partial trisomia 8 Partial trisomia 14 | 28 | 22 | Abnormal USG |
| 6 | 47, XY, +21 | Classical Down Syndrome | 28 | 22 | High risk at triple test |
| 7 | 46, XY, t(10;12)(q22;q22) | Balanced translocation | 27 | 20 | Bad obstetric history |
| 8 | 47, XX, +18 | Trisomia 18 | 34 | 22 | Abnormal USG |
| 9 | 47, XX, +9 | Trisomia 9 | 42 | 24 | Advanced maternal age |
| 10 | 47, XX, +18 | Trisomia 18 | 29 | 31 | Abnormal USG |
| 11 | 46, XX, del(3)(p25pter) | 3p partial deletion | 29 | 21 | Abnormal USG |
| 12 | 47, XY, +21 | Classical Down Syndrome | 37 | 19 | Advanced maternal age |
| 13 | 47, XY, +13 | Trisomia 13 | 42 | 29 | Advanced genetic analysis |

widely applied in the world from 16th gestational week up to term, some researchers reported that it could be applied beginning from 14th week.[8-10] In our study, the earliest gestational week is 15 and the most advanced gestational week is 38th week. There was fetal anomaly in the case which was applied cordocentesis at 15th week and termination was being considered.

Cordocentesis is one of the methods widely accepted for prenatal diagnosis. The high rate of complications associated with initiative is one of the most important issues about approving this process. The most significant complication of cordocentesis is fetal loss. In various series, fetal loss rates was reported between 1.9% and 3.1%.[11,12] Fetal loss rates depends on background fetal pathologies as well as the initiative. It is emphasized that fetal losses associated with the process are seen frequently within first 2 weeks.[13] It was reported in studies that fetal loss rates depend on gestational week that cordocentesis is applied, experience of physician, cordocentesis indication and cordocentesis field. Ghidini et al.[14] grouped cordocentesis cases as low-risk and high-risk groups in terms of fetal loss possibility and reported that there was no cases with chromosomal anomaly, growth retardation, intrauterine infection and non-immunohydrops in the low-risk group. In the study of Acar et al.[15] which evaluated 250 cordocentesis cases, fetal loss rate was found as 4.8%. In another study which evaluated fetal losses in the midgestational period associated with cordocentesis, 1020 cases of cordocentesis group was compared with 1020 cases of control group and fetal loss rate was found as 3.2% and 1.8%, respectively.[16] In our study, fetal loss after process was not detected during the acute period and we could not evaluate long-term results of most of the cases since their follow-ups were maintained in the centers they were referred to after the process.

The first preference for initiative region of cordocentesis cases is the area near placental tip of umbilical cord. If placental location is not appropriate, free umbilical cord may be tried. However, there is maternal blood contamination risk in blood samples taken from the point where the cord enters into placenta.[17] Although there were maternal blood contamination in 5 of cases taken blood from placental insertion, no contamination was found in other cases inserted through free cord.

While the initiative was unsuccessful in 8 of 259 cordocentesis cases due to technical rea-

sons, it was repeated in 7 due to maternal contamination and non-existence of reproduction in the culture. Karyotype analysis was performed on totally 251 cases and our success rate was 96.9%. The success rate in the series of Weiner was reported as 95% in the literature while it was 98.5% in the series of Shalev and 98.8% in the series of Acar et al.[8,18,15]

During initiatives, maternal obesity, agitation, oligohydroamnios and posterior located placenta were observed as the factors complicating initiative. However, including 4 cases that had intrauterine transfusion, there was no need to sedate mother, to apply medication for reducing fetal movements or to perform local anesthesia instead of abdominal entry.

Intraamniotic bleeding is a frequent complication observed by all researchers who perform cordocentesis study. While Daffos[11] observed intraamniotic bleeding in 41% cases in the wide series of 606 cases, it was reported that bleeding duration was less than 2 minutes in 38% of cases. Weiner stated the rate of intraamniotic bleeding between 29% and 42% in his series.[8] Acar et al reported intraamniotic bleeding rate as 27.6%.[15] In the cordocentesis series of 1320 cases applied by Tongsons et al. between 16th and 24th weeks, bleeding rate was reported as 20.2% and the duration longer than one minute was 5.2%.[19] Limited amount of intraamniotic bleeding was observed in 77 of 259 cordocentesis initiatives (30%) after the process. This rate is compatible with the literature. All these bleedings took 2 minutes or less and stopped spontaneously.

Fetal bradycardia after cordocentesis is relatively a frequent and serious complication with significant prognostic value.[20] Jauniaux21 reported fetal bradycardia rate after initiative as 10% and Acar et al.[15] reported it as 9%. In our cases, bradycardia was developed after the process in 6.1% of the cases; however, bradycardia was a temporary situation in all cases and they were gone by themselves.

Fetal karyotyping success by cordocentesis is about 90%.[22] In our patient group, this rate was found as 96.6% (251/259). In our study, chromosome anomaly was detected in 13 (5.2%) of 251 cordocentesis cases who had karyotype analysis. In 10 (4%) of cases who were detected chromosomal anomaly had numerical anomaly, 2 (0.8%) of them had structural anomaly and one of them (0.4%) had both numerical and structural anomaly. Advanced maternal age is a risk factor for numerical chromosome anomalies.[23] When cordocentesis indications and detected fetal chromosomal anomaly incidence are compared in our study, it is seen that advanced maternal age is placed on the top. Chromosomal anomaly was detected in 4 (14.2%) of cases who had cordocentesis by advanced maternal age indication. Although advanced maternal age has not been a cordocentesis indication anymore in many advanced countries, establishing invasive genetic diagnosis associated with advanced age is still disputable.

8.9%-27.1% chromosomal anomaly was reported in cases with pathological USG diagnosis.[24,25] In our patient group, chromosomal anomaly was found in 6 cases (6.1%) of 98 cases with abnormal fetal ultrasonography diagnosis. The cause for such low rate is that a significant part of our cases have pathologies together with low rates of chromosomal anomaly such as single umbilical artery.

Trisomia 21 karyotype was found in 5 (2%) cases. NT increase with pathological USG diagnosis was found in one of these cases. While the pathological USG findings of cases (2 cases, 0.8%) detected Trisomia 13 karyotype were single umbilical artery, holoprosencephaly, microphthalmia, hypoplastic left ventricle and hypotelorism, the pathological USG findings of cases (2 cases, 0.8%) detected Trisomia 18 karyotype were omphalocele, single umbilical artery, IUGR, ASD (atrial septal defect) and VSD (ventricular septal defect).

In a case performed cordocentesis due to short femur at fetal USG, 47,XX,t(8;14)(p22;q21),+der(14)(8;14) karyotype was detected. Genetic consultation was provided to the

family. The family willingly decided to continue the pregnancy. No information could be received from the family after the delivery. Maternal balanced translocation carriage was detected after the parental karyotype analysis. The case was defined for the prenatal diagnosis in the literature in terms of translocation broken regions and chromosome establishment.

The requirement for karyotyping cases with fetal single umbilical artery should be discussed. In our series, 46,XX,del(3)(p25pter) karyotype was detected in a case that was performed cordocentesis due to single umbilical artery at fetal USG. The family decided to stop the pregnancy. Same karyotype was confirmed in the chromosome analysis performed on postmortem fetal tissue culture. Hamartomatosis structures in brain, and growth defects at kidney, lung, liver and pancreas were found by autopsy. The case is the first fetus which was detected single umbilical artery at fetal USG together with 3p partial deletion at prenatal diagnosis.[26,27] There are also other studies justifying to perform invasive initiation at single umbilical artery. Clinical situations and findings that may be observed with single umbilical artery are IUGR, renal, cardiac anomalies.[28] Also, there is increased Trisomia 18 risk.[29] On the other hand, short femur cases should be examined in detail and genetic evaluation should be done in the existence of additional major or minor anomaly. However, if skeletal dysplasia is detected after detailed examination, genetic diagnosis should be abandoned; femur and humerus nomograms may change according to societies. As long as prospective studies are not performed by taking nomograms of our society into consideration, limits published in other countries would be misleading.

## Conclusion

At experienced hands and when optical cultural conditions are provided, cordocentesis is an invasive diagnosis method that can be applied with high accuracy and safety. Though traditional techniques such as amniocentesis and CVS are still popular in fetal diagnosis, fetal blood sampling has a critical role in chosen cases where other techniques are unsuccessful.

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# Adnexal Masses In Pregnancy: A Series of 12 Patients

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**Abstract**

**Objective:** The aim of this study was to evaluate the clinico-pathological features, rate of complications and pregnancy outcomes of pregnancy-associated adnexal masses.

**Methods:** A total of twelve patients were admitted to our clinic with diagnosis of adnexal mass in pregnacy during this period. Eleven of the twelve patients have been operated. Four of eleven patients (33,3 %) needed an emergency surgical intervention due to clinical signs and symptoms of acute abdomen. Three of these cases (25%) were diagnosed as adnexal torsion. Seven of the patients (58.3%) were operated under elective conditions. The most common histopathological diagnosis was dermoid cyst (27.3%) and mucinous cystadenoma in 27.3% of cases. None of the cases were malignant. None of the patients had an adverse pregnancy outcome due to emergency laparotomy.

**Results:** A retrospective study was designed to review the medical records of cases of adnexal masses in pregnancy that admitted to our tertiary center clinic between November 2006 and August 2009.

**Conclusion:** Conservative management can be preferred in pregnancy associated adnexal masses which don't cause acute abdomen and do not have the signs of malignity with clinical evaluation and imaging methods.

**Keywords:** Pregnancy, adnexial masses, management.

*Gebelikte adneksiyal kitleler: 12 vakalık seri*

**Amaç:** Bu çalışmanın amacı gebelik ile ilişkili adneksiyal kitlelerin klinikopatolojik özelliklerini, komplikasyon oranlarını, gebelik sonuçlarını değerlendirmektir.

**Yöntem:** Kasım 2006-Ağustos 2009 tarihleri arasında bir tersiyer merkez olan kliniğimize başvuran, gebelikte adneksiyal kitle olgularının medikal kayıtları incelenerek retrospektif bir çalışma tasarlanmıştır.

**Bulgular:** Bu dönemde toplam 12 hasta gebelik ve adneksiyal kitle tanısı ile merkezimize kabul edilmiştir. 12 hastanın 11'i opere edilmiştir. 11 hastanın 4'ü (%33.3) akut karın belirti ve klinik bulguları ile acil cerrahi girişime ihtiyaç duymuştur. Bu vakaların 3'ü (%25) adneks torsiyonu tanısı almıştır. Hastaların 7'si (%58.3) elektif koşullarda opere edilmişlerdir. En sık karşılaştığımız histopatolojik tanı dermoid kist (%27.3) ve müsinöz kistadenomdur (%27.3). Olguların hiçbirinde malignitey rastlanmamıştır. Hastaların hiçbirinde acil laparotomiye bağlı olumsuz gebelik sonucu görülmemiştir.

**Sonuç:** Akut karın gelişmeyen, klinik ve görüntüleme yöntemleri malignite lehine olmayan gebelikle ilişkili adneksiyal kitle olgularında gözlemsel yaklaşım tercih edilebilir.

**Anahtar Sözcükler:** Gebelik, adneksiyal kitle, yönetim.

## Introduction

Adnexal masses in pregnancy are not rare or unusual findings. They are observed more frequently after the routine use of obstetric ultrasonographic examination for evaluation of pregnancy. The incidence of adnexal masses in pregnancy is estimated to be between 1% and 2%1. Most of them are corpora lutea which are

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physiological conditions in pregnancy and tend to resolve spontaneously at the begining of the second trimester. Most clear cysts having less than 5 cm diameter are usually functional and can be managed expectantly as they also resolve by 16 weeks of pregnancy2. An adnexal mass persisting beyond 16 weeks of pregnancy needs to be considered for risks of torsion, tumor rupture and obstetric risks such as abortion, preterm labor and delivery, obstruction of labor, rupture of membranes3. Additionally, such a condition carries the risk of malignant disease. The incidence of ovarian malignancy is reported to be as high as 2 to 6% among all adnexal masses diagnosed during pregnancy4. The tumor antigen CA-125 has a limited value due to its elevated and fluctuating level in normal pregnancy and the other markers such as ,-hCG and alpha-fetoprotein are routinely used for fetal surveillance rather than tumor detection during pregnancy5. There is still a controversy regarding the optimal management option, whether it should be in the form of expectant management or surgical intervention, for an adnexal mass diagnosed during pregnancy due to possible fetal risks and surgical morbidity on one hand, and the risk of need for emergency surgery and delay in the diagnosis of malignancy when expectant management is chosen, on the other hand3. We conducted a retrospective review of the patients with adnexal masses some of whom operated during pregnancy and evaluated the pathological features, rate of complications and outcome of the pregnancies.

## Methods

A retrospective study was designed to review the medical records of cases of adnexal masses in pregnancy that admitted to our tertiary center clinic between November 2006 and August 2009 . There were totally 3306 deliveries during the period of the study. Age, gravidity, parity were noted. Gestational weeks at the time of diagnosis, gestational age at the time of delivery and at the time of surgery (if surgery is performed) were collected according to date of the first day of last menstrual period and if those were missing, depending on the ultrasonographic fetal biometry at the first trimester. Three dimensional diameters of the masses in milimeters were measured sonographically and the mean sizes were calculated by division of sum of these three diameters into three. Cases were divided into two according to the indication of the surgery, whether they are emergent or elective. The ultrasonographic findings of masses such as septations and papillary projections were noted. Complaints of the patients for hospital admission (if they existed), serum CA-125, β-hCG and alpha-fetoprotein levels were collected. The surgical aspects, type of delivery (C-section and vaginal delivery), postoperative complications such as PPROM and preterm labor and the treatment modalities for postoperative complications were established. Birth weight and gender of babies, apgar scores at the first and the fifth minutes, perinatal and neonatal complications were defined. Finally, pathological diagnosis of surgical specimen and frozen section specimen (if they were needed to be sent to the pathology department intraoperatively) were noted from the pathological examination reports. Values were expressed as mean±SD (standard deviation) unless stated otherwise.

## Results

A total of twelve patients were admitted to our tertiary center clinic with diagnosis of adnexal mass in pregnacy between November 2006 and August 2009. The mean maternal age

was 24.1±3.8 years (range 19-31 years). The mean gravidity was 1.9±0.99 (range 1-4) and mean parity was 0.67±0.78 (range 0-2). The median gestational weeks at the time of diagnosis of the adnexal mass and at the time of the surgery was 8 weeks and 3 days (range 5 weeks 5 days to 38 weeks 2 days) and 20 weeks (range 7 weeks to 38 weeks 6 days) respectively. The mean time of delivery was 37 weeks (range 32 weeks to 38 weeks 6 days). The mean birth weight was 3165±644 grams (range 2260 to 4110 grams). The mean first minute Apgar score was 7.5±1.4 (range 5 to 9) and the fifth minute was 8.7±1.0 (range 7 to 10) (Table1). The mean size of the masses were 87.83±48.18 milimeters (range 41 mm to 210 mm). Serum CA-125 levels were assessed in nine of twelve patients and the mean level was 41.78±37.0 IU/ml (referance range 0 – 35 IU/ml) (range 11 to 130 IU/ml). As a sum, eleven of the twelve patients have been operated. Four of eleven patients (33.3%) needed an emergency surgical intervention due to clinical signs and symptoms of acute abdomen. Seven of the patients (58.3%) were operated under elective conditions. In emergent cases, one was diagnosed at 31. week with the presenting symptom of abdominal pain. There was a 132 mm hypoechoic cystic mass in the left adnexa sonograhically. She had two previous cesarean sections. This patient admitted to the emergency department with severe abdominal pain and uterine contractions at 35. week. Cesarean and left oophorectomy was performed concurrently. Frozen section and final pathology report revealed a mucinous cyst adenoma. Three of these cases were diagnosed with the clinical symptoms and signs of adnexal torsion, two of which were the torsion of an ovarian mass (one was simple cyst and the second was hemorrhagic cyst) and one was isolated tubal torsion. Two of these patients underwent surgery at the first tirmester and the one (isolated tubal torsion) in the third trimester. Two of the emergent cases were operated just after the diagnosis of the adnexal lesion because the clinical presentation was adnexal torsion. One of them was 30 week and 1 day, there was a 73 mm multiloculated hypoechoic cystic mass with incomplete septations in the right adnexal region diagnosed with sonograhy. At laparotomy right ovary was appeared normal while the right fallopian tube was twisted two times around itself. The intraoperative findings at the emergent laparotomy were consistent with the isolated right tubal torsion. The fallopian tube was not seemed necrotic, so detorsion was done. 2 weeks later at 32. gestational week this patient admitted to the emergency department with regular uterine contractoins, 3 cm dilatation and 50% effacement. With the indication of breech presentation, cessarean section was performed and 2700 gr baby was born. The other case was diagnosed and operated at the nine week two days. The presenting symptom of this patient was abdominal pain. A 58 mm bilobulated hypoechoic cystic

**Table 1.** Information on maternal and neonatal.

| | |
|---|---|
| Maternal age (year) | 24..1±3.8 (19-31) |
| Nulliparous n (%) | 6(%50) |
| Parity=1 n (%) | 4(%33) |
| Parity=2 n (%) | 2(%17) |
| gestational age (week)* | 37(32-39) |
| Full-term delivery n (%)† | 8(%80) |
| Preterm delivery n (%)† | 2(%20) |
| Birth weight (g)* | 3165±644 (2260-4110) |
| Apgar score | |
| 1. dk* | 7.5±1.4 (5-9) |
| 5. dk* | 8.7±1.0 (7-10) |

†*Ortalama±standart sapma (minimum-maksimum) olarak verilmiştir.
†2 hasta takipten kayboldu.

mass was diagnosed by sonography. CA-125 value of this patient was not studied due to urgent conditions of the operation. Intraoperative diagnosis was ovarian torsion. The final pathology report of this patient revealed necrotic hemorrhagic corpus luteum. This patient was lost to follow up after the operation. The other emergent case was diagnosed at 6 week and 5 day. There was a multiseptated anoekoik kistik lesion in the right adnexal region. At 10 week and 4 day this patient was admitted to the emergency department with the clinical signs and symptoms of acute abdomen. A laparotomy was made with the diagnosis of adnexal torsion. Intraoperatively right ovary was twisted around the infundibulopelvic ligament. The ovary was appeared edematous and hemorrhagic but not necrotic. So detorsion of the ovary and cystectomy was done. This patient had undergone elective cesarean at 38 week and 6 day and 2630 gr baby was born. There were 7 cases operated under elective conditions. Six of these seven patients were diagnosed at the first trimester by routine obstetric ultrasound examination. One of them was diagnosed at the third trimester. Three patients were operated in the first trimester, in one of the patients, surgery was delayed to second trimester. The remaining three patients including the patient diagnosed at the third trimester were operated during the cesarean section. In one of the patients, bilateral multiple simple ovarian cysts among which the biggest having the mean size 72 mm were diagnosed at the eleventh week. The appearance of ovaries was just like in the ovarian hyperstimulation syndrome, but there was no ascites and the conception was spontanous. These cysts have resolved during the course of pregnancy spontaneously, no surgery was intended for this patient. During the cesarean section, no adnexal mass was found. Two of the patients were lost to follow-up after the operation for adnexal mass. Eight of the remaining ten patients were delivered by cesarean section (80%) and two patients (20%) were delivered vaginally. Two of the patiensts operated under emergent conditions had preterm labor. One is the patient with isolated tubal torsion operated at 30 week and one day. At 32. week she had preterm labor. Due to breech presentation she had undergone cesarean section. The other one is the emergent patient with mucinous cyst adenoma who is operated at 35. week and had a cesarean at the same time. In three cases (27.3% of all cases), pathological diagnosis was mucinous cystadenoma. In the other three (27.3 % of all cases), the diagnosis was dermoid cyst (mature cystic teratoma). There was three adnexal torsion cases, one was torsion of right fallopian tube, two were torsion of benign simple cyst and hemorrhagic corpus luteum. In two cases, the pathologic diagnosis was paraovarian cyst (Table 2).

## Discussion

In our series, 3 of 12 patients (25 %) required an urgent laparotomy with indication of adnexal torsion. One of them was isolated tubal torsion. The other two adnexal torsion cases had the diagnosis of corpus luteum and benign-functional cyst after the pathological examination. The rate of torsion reveals a great variability among the series, from 1 % to 22 %6. Adnexal torsion usually presents in the first trimester, as the uterus is moving out of the pelvis, although some cases have been described in the second and, rarely, in the third trimester. The most common pathological diag-

**Table 2.** Clinical characteristics of patients.

| | Not emergency/ elective-operation time | Week of diagnosis, complaints, clinical signs | Ultrasound findings | operation week | indication for surgery | Applied Surgical Results | Frozen | Final pathology | Week of birth, type, indication |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Emergency childbirth third trimester | 31 weeks, groin pain, acute abdomen, 23y, G3P2Y2 | 132 mm hypoechoic left adnekste | 35 weeks | Severe pelvic and abdominal pain, preterm labor, previous | oophorectomy + appendectomy | Mucinous tm | Mucinous cystadenoma | 35 weeks, repeated painful |
| 2 | At diagnosis in emergency (third trimester) | 30 weeks 1 day, severe abdominal pain, acute abdominal findings 20y, G1P0 | Right adnekste 73 mm multiloculated hypoechoic cystic mass with incomplete septation | 30 weeks 1 day | Adnexa torsion | detorsion + salpingostomi, isolated from the right tubetorsion, | — | — | 32 weeks, C/S in pretermaction, breecharrival |
| 3 | Emergency-the time of diagnosis (First trimester) | 9 weeks 2 days, abdominal pain, acute abdomen, 30Y,G4P2A1Y2 | The right ovary 58 mmbilobüle hypoechoiccystic mass | 9 weeks 2 day | Ovarian torsion | Right ovarydetorsiyonu, Right ovarian cystexcision, ovarian torsion, 6 cmhemorrhagiccystic mass | — | hemorrhagiccorpus luteum | Lost to follow-up, repeat C/S |
| 4 | Emergency-lovers after a month (First trimester) | 6 weeks 5 days, acute abdomen, 22y, G1P0 | 70 mm multiseptali, cystic mass | 10 weeks 4 day | Ovarian torsion | detorsion, cystectomy, ovarian edemaand hemorrhagic, not necrotic | benignfibrous wall | Benign cystswall | 38 weeks 6 days, elective C/S |
| 5 | Elective-First trimester (diagnosisa weekafter) | 8 weeks 3 days,acute abdomen 22y, G2P1Y1 | 210 mm, hypoechoiccystic mass, mucinouscyst adenoma? | 9 weeks 5 day | Abdominal pain, suspicious for malignancy, large mass, CA125: 130 | Right oophorectomy,appendectomy,provide the ksifoideranging from 25x15cm mass (normalovarian tissue observed) | mucinous tumor,benign malign separation paraffin block | Mucinous cyst adenoma | 37 weeks 3 days, pain fulrepeat C/S |
| 6 | Elective-First trimester (diagnosisat the time) | 7 weeks acute abdomen 26y, G1P0, | 62 mm, miksekoik | 7 weeks | severe abdominalpain, torsion The risk of torsioncould not be ruled out | myomectomy | — | Leiomyoma uteri | Lost to follow-up, on the outer center |
| 7 | Elective-second trimester (diagnosis after 6 weeks) | 7 weeks, 2 days, No complaints, control, 26y, G2P1Y1, | 76 mm, hypoechoic, miksekoik, dermoid? | 13 weeks 1 day | Mass 76 mm Growth of 85 mm,forward groin pain The risk of torsion | Cystectomy | mature cystic teratoma | mature cystic teratoma | Term, normal birth |
| 8 | Elective-second trimester (diagnosis after 15 weeks) | 5 weeks 5 days, No complaints, control, 29y, G2P1Y1 | 64 mm, miksekoik, dermoid? | 20 weeks | Mass 64 mm Growth of 88 mm, The risk of torsion, a largemass | Left USO *(Normal ovariantissue observed) | mature cystic teratoma | mature cystic teratoma | Term, normal birth |
| 9 | Elective-birth | 7 weeks 5 days, No complaints, control, 24y, G2A1Y0, | 41 mm hypoechoic, content of heavy oilcompatible with papillarystructure, dermoid? | 38 weeks 1 day | During caesarean cystectomy | caesarean + cystectomy | — | Dermoid cyst | 38 weeks1 day, elective C / S |
| 10 | Elective-birth | 38 hft 2 gün, dış merkezden sevkli, ağrı, 19y, G1P0 | 138 mm, anekoik kist | 38 weeks 3 day | During caesarean cystectomy | Caesarean +cystectomy, left 20x15 adnekstemm para ovaryan cystic lesion observed) | — | benign cysticformation (para ovaryan cyst) | 38 weeks 3 days, elective C/S, painful, largeadnexal mass |
| 11 | Elective-birth | First trimester (36 weeks1 day, whileguided), complaints No, control, 31y, G3P1A1Y1 | 58 mm, septate, multiluküle | 38 weeks 6 day | During caesarean oophorectomy | Caesarean +oophorectomy +appendectomy (Normal ovariantissue was observed) | Benign müsinöz kist | mucinous cystadenoma | 38 weeks6 days, repeat C/S |

*****Abbreviations: **C/S:** Caesarean, **USO:** Unilateral salpingooforektomi

noses were dermoid cyst (mature cystic teratoma) and mucinous cystadenoma. The other pathologically reported cases were paraovarian cyst, benign-functional ovarian cyst and hemorrhagic corpus luteum. In literature dermoid cysts are the most common types of adnexal masses in pregnancy and tend to result in torsion more commonly. They comprise approximately 37% of all adnexal masses diagnosed during pregnancy. Cystadenomas are seen as 24 %, persistent corpus luteum cysts as 20 %, paraovarian cysts as 5 %, endometriomas as 5 %, leiomyomas as 5 %. Malignant tumors are found in upto 5,9% of the cases.[7] In our series, we found no evidence of malignant disease. Also, no sonographic criteria for risk of ovarian malignities such as solid mass, nodular appearance, thick septations were observed in any of the cases. The incidence of malignancy for adnexal masses in pregnancy was estimated to be as high as 6.8%8. In our case series, we did not encounter any malignant cases. The management of adnexal masses during pregnancy is still a controversial issue. Surgery and observation of the mass are the two management options, but there is not a standard established protocol for those patients. Surgery is the preferred way of treatment when malignancy is suspected or there is the risk of torsion, cyst rupture or labor obstruction. Sometimes, observation of the lesion may be the optimum way of management to avoid maternal morbidity and adverse fatal-neonatal outcomes. In our series, we performed surgery for 11 of the 12 patients. Four of them were performed under emergency circumstances. Three of them presented with adnexal torsion and one of them presented with signs of the acute abdomen and had a mass of 132 mm diameter. There were no significant difference between emergent and elective surgery groups according to maternal and fetal-neonatal outcomes. Results of similar series are consistent with ours when the perinatal outcomes of emergent and elective surgery were compared. Also, no postoperative complications and maternal morbidity is observed in our series.

**Table 3.** Pathological features of adnexal masses (n=11).

| | Olgu sayıları | |
|---|---|---|
| Pathological diagnosis | **n** | **%** |
| Mature cystic teratoma | 3 | 27.3 |
| Mucinous cystadenoma | 3 | 27.3 |
| Paraovaryan cyst | 1 | 9.1 |
| Myoma uteri | 1 | 9.1 |
| Simple cyst (basic) | 1 | 9.1 |
| Hemorrhagic corpus luteum | 1 | 9.1 |
| Isolated tubal torsion | 1 | 9.1 |

## Conclusion

Majority of adnexal masses that observed in the first trimester are corpus luteum cysts and they are expected to resolve spontaneously at the begining of the second trimester. Adnexal masses persisting beyond the second trimester need to attract attention especially due to their risks of torsion and rupture and potential obstetrical risks they carry. Also, there is a risk of missing the underlying malignancies. Although, no maternal or fetal-neonatal adverse outcome is reported in this series, surgical point of view must be limited in patients having the risks previously mentioned. Conservative management can be preferred in pregnancy associated adnexal masses which don't cause acute abdomen and do not have the signs of malignity with clinical evaluation and imaging methods. Further studies and larger series are needed to have more clear guidelines on management of adnexal masses in pregnancy which is still a challange and issue of controversy.

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# An Anaplastic Astrocytoma Which is Diagnosed in Pregnancy: A Case Report

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**Abstract**

**Objective:** Astrocytoma, central nervous system called astrocytes small, star shaped glial cells, glialderived and the most common malignant tumors. We discussed the management of anaplastic astrocytoma, which was first diagnosed in the 26th gestational week, in the highlights of the literature.

**Case:** 28 year old patient, in 26th gestational week was admitted to our hospital with persistent headache, numbness in the left side-of the body and neck swelling. As a result of Magnetic Resonance Imaging, a cranial tumor located in the anterior of the medulla oblangata was diagnosed. In 27th gestation week, extramedüller cervical intradural tumor excision was performed. The patient was delivered by cesarean section in 34th gestational week. After cesarean section, radiotherapy treatment was started.

**Conclusion:** Patients with anaplastic astrocytoma are rare in pregnancy. To help the management of this patients, new, largescale case series are needed. For the best obstetric and neurological results, treatment is carrıed out in tertiary centers with multidisciplinary approach.

**Keywords:** Anaplastic astrocytoma, pregnancy, multidisciplinary approach.

*Gebelikte tanı alan anaplastik astrositoma: olgu sunumu*

**Amaç:** Astrositomlar, merkezi sinir sistemindeki astrosit adı verilen küçük, yıldız şeklindeki glial hücrelerden köken alan kötü huylu ve en sık görülen glial tümörlerdir. 26. gebelik haftasında tanısı konulan maternal anaplastik astrositoma olgusunun takip ve yönetimini literatür bilgileri ışığında tartıştık.

**Olgu:** 28 yaşında hasta, 26. gebelik haftasında persiste eden baş ağrısı, sol kolunda ve bacağında uyuşma, boyunda şişlik şikayetleri ile kliniğimize başvurdu. Manyetik Rezonans görüntüleme sonucunda hastaya, medulla oblangata yerleşimli kranial tümör ön tanısı konuldu. Hastaya, 27. gebelik haftasında servikal intradural extramedüller tümör eksizyonu yapıldı. Hasta, 34. gebelik haftasında sezaryen ile doğurtuldu. Sezaryen sonrasında radyoterapi tedavisine başlandı.

**Sonuç:** Gebelikte nadir görülen anaplastik astrositoma olgularının yönetiminde yardımcı olacak, yeni, geniş ölçekli olgu serilerine ihtiyaç vardır. En iyi obstetrik ve nörolojik sonuçları elde etmek için tedavi, tersiyer merkezlerde ve multidisipliner yaklaşımla gerçekleştirilmelidir.

**Anahtar Sözcükler:** Anaplastik astrositoma, gebelik, multidisipliner yaklaşım.

## Introduction

Astrocytomas are the most common malignant glial tumors originated from small star shaped glial cells called astrocytes within central nervous system. Anaplastic astrocytomas (AA) are defined as grade 3 glial tumors according to the classification made by WHO in 2000. While the incidences of multi-formed glioblastoma and anaplastic astrocytoma were 0.2-0.5 in 100,000 for those 14 years old, it is 4-5 in 100,000 for those over 45 years old. The localization of anaplastic astrocytomas varies

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according to age. While most of them locate at cerebellum below 25 years old, it is frequently located at cerebral over 25 years old.[1]

AA generally appears sporadically without any definable environmental factor or any genetic familiarity. AA is more frequent in women than men. At the same time, it is more frequent in white race than black race.

In AA, symptoms of clinical classical intracranial pressure increase (headache, vomit, conscious disorders, 3rd and 6th cranial nerve involvements) are frequently observed as in other intracerebral lesions. High phased astrocytic tumors do not cause hydrocephaly since they generally do not locate at ventricle. Neurological deficits appear depending on the location zones. Appearance of epileptic findings due to irritative effect is frequent in frontal and temporal located tumors. Classically, headache, epileptic seizure and hemiparesis triad are seen more than half of the cases.[2] Although primary intracranial tumors are rarely seen in women between 20 and 39 years old, it is at the fifth rank among cancer-related deaths.[3] While glial tumors are the most frequent tumor types among this age group, followed by meningiomas and acoustic neurinomas.[4] When women who are pregnant and who are not pregnant at same ages, no difference was found among primary brain tumor incidence.[5]

Standard treatments of AA are surgical and postoperative radiotherapies. High dose of radiotherapy, adjuvant chemotherapy, alternative fraction regimes, heavy particle treatment, interstitial brachytherapy and radiosurgery are used as different treatment modalities in order to elongate survival period.[12] However, a consensus have not been reached as there is no data except case series within the literature about the patient management during pregnancy.

In our case, we discussed the follow-up and management of maternal anaplastic astrocytoma diagnosed during pregnancy in terms of literature.

## Case

The 28-year-old patient with Gravida 3, Parity 2 applied to our clinic at her 26th gestational week for complaints of persisting headache, numbness at her left arm and leg and swelling on her neck. There were two cesareans on her obstetric history. First baby was lost due to hydrocephaly when two years old. At her first trimester scanning test who had her follow-up at an external center, free beta-hCG was 39.3 ng/mL (1.00 MoM), PAPP-A was 6.3 mIU/mL (2.75 MoM) and nuchal transparency was 1 mm. According to these values, Down syndrome combination risk at first trimester scan was calculated as 1/8236.

At 26th gestational week, the patient was consulted with neurosurgery department due to her neurological complaints. At her neurological examination, there was hoarseness; motor forces were found as distal 4/5 and proximal 3/5 at her upper extremity and as 3/5 at her lower extremity. Motor forces were distal 2/5 and proximal 1/5 at her left upper extremity and 3/5 at her left lower extremity. Left lower extremity was found as hypoesthesic and left upper extremity as distal anesthetic and proximal hypoesthesic. The mass compressing spinal cord on medulla oblongata C2-C3 level was observed on Magnetic Resonance Imaging (MRI). The patient was established the preliminary diagnosis as medulla oblongata located cranial tumor (Fig. 1). Twenty-four mg/day methylprednisolone was administrated to the patient in order to decrease the distinctive edema around the mass and to reduce clinical symptoms. The patient was hospitalized at the neurosurgery department and followed by weekly perinatological consultation. An operation was decided when mental confusion and shortness of breath developed despite the methylprednisolone administration. As the patient was under a high dose of methylprednisolone treatment, betamethazone treatment was not additionally applied in terms of fetal lung maturation. Before operation, 250 mg hydroxyprogesterone capronate was applied to

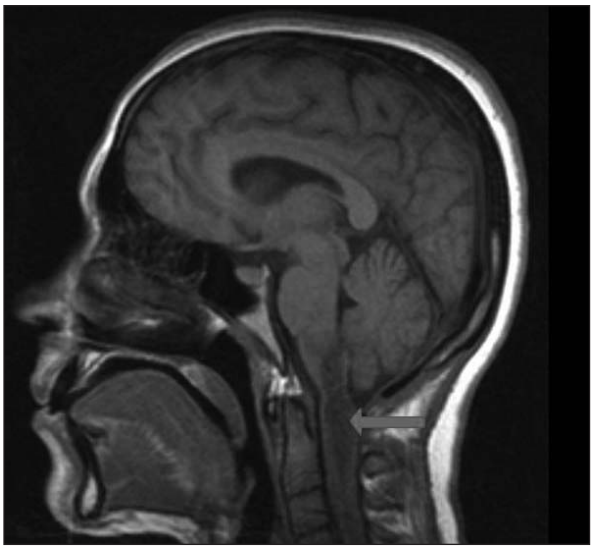

**Figure 1.** Preoperative view of anaplastic astrocytomas located at medulla oblongata.

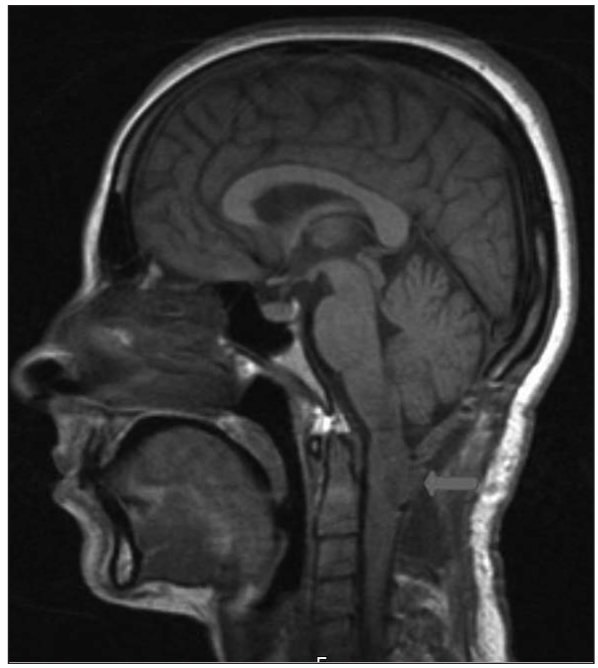

**Figure 2.** Postoperative view of anaplastic astrocytomas located at medulla oblongata.

the patient intramuscularly before the operation for early labor prophylaxis. Cervical intradural extramedullary tumor excision was done at her 27th gestational week. Tumor was removed completely (Fig. 2). Fetal well-being before the operation was checked by ultrasonography and umbilical artery Doppler (Pulsatility Index: 0.79 and Resistance Index: 0.51). Methylprednisolone treatment was maintained for two weeks after the operation. She was followed up for 3 days in intense care unit in the neurosurgery department during postoperative period. Pathology result was reported as anaplastic astrocytoma (WHO grade 3) observed as 4 mitoses at 4 large enlargement areas displaying hypercellularity and distinctive plemorphism (Figure 3).

The patient was evaluated by neurosurgeons via pathology results and it was decided to apply radiotherapy. The patient was consulted by perinatology department in terms of radiotherapy during pregnancy. It was evaluated again with neurosurgery department to postpone radiotherapy at least until 34th gestational week of patient who was not detected any pathology during obstetric examination. At the end of consultation, it was decided to postpone radiotherapy to postnatal period. The patient was taken into weekly follow-up at the perinatology department.

At the examination performed on 30th gestational week, biparietal diamtere was measured as 75 mm, head circumference as 271 mm, abdominal circumference as 242 mm, femur length as 56 mm, approximate birth weight as 1362 gr, pulsatility index at umbilical

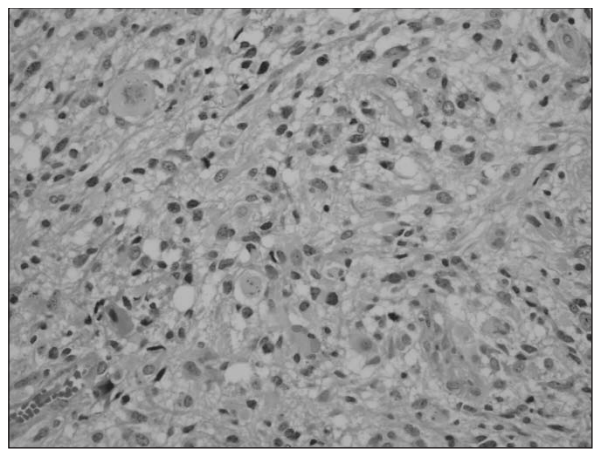

**Figure 3.** Anaplastic astrocytomas (WHO Grade 3).

artery Doppler as 0.81 and resistance index as 0.52. Amniotic fluid volume was at normal limits and placenta was posterior wall located. The patient was hospitalized for follow-up after 32nd gestational week. Fetal well-being was followed by daily non-stress test (NST) and umbilical artery Doppler. There was a distinctive muscle weakness on left side of the patient.

At the end of 34th gestational week, 2280 gr live singleton boy baby was delivered by cesarean under general anesthesia. 1st minute Apgar score was 6, and 5th minute Apgar score was 8. Bilateral pomeroy type tube ligation was performed during operation. The baby was followed up in newborn intensive care unit for 19 days after delivery. The baby did not need surfactant and discharged in good condition without any neonatal complication. No postoperative early or late complication was observed in the patient and discharged on her postoperative 3rd day.

Residue lesion with 2-3 mm diameter was detected on medulla oblongata level via MRI performed on postoperative 5th day. There was minimal edema around the lesion. 5 cures of radiotherapy were applied to the patient beginning from postoperative 7th day. Concomitantly, 8 mg/day dexamethasone treatment was initiative. The follow up of the patient is still performed in a multidisciplinary way by radiation oncology, neurosurgery and medical oncology departments. The follow-up of the baby is maintained by our well child polyclinic and no pathological finding has been detected.

## Discussion

The management of intracranial tumors during pregnancy differs clinically. Intracranial tumors the most frequently observed in women at their reproductive periods are glial tumors followed by meningiomas and acoustic neurinomas.

Pregnancy does not cause any increase in the risk of brain tumor. However, pregnancy affects the biological behaviors of glial tumors, meningiomas, vascular tumors and pituitary adenoma. This may cause differentiation in appearance time of first symptoms and development rate of symptoms.[6] Tumors behave different in different periods of pregnancy. Glioms often appear at first trimester while spinal vascular tumors appear at third trimester.[7]

In our case, the patient applied to our clinic at her 26th gestational week due to the complaints of headache and numbness at her left upper and lower extremities. These complaints associated with the intracranial pressure were compatible with the case series in the literature. While it is expected that tumor is generally located at cerebral hemisphere at reproductive period, a mass located at medulla oblongata was observed in our case. No neural deficit was observed at the neurological examination of our case except motor force loss at left upper and lower extremities and hoarseness.

Upon the detection of medulla oblongata located tumor and edema around lesion via MRI, 24 mg/day methylprednisolone was administrated. Upon the development of mental confusion and shortness of breath despite the treatment, an operation was decided. Cervical intradural extramedullary tumor excision was performed at her 27th gestational week. Fetal well-being was checked by ultrasonography and umbilical artery Doppler before and after the operation. Fetal heart rate during the operation was followed up by hand Doppler device hourly. When the literature was researched, intraoperative fetal monitorization was performed to the patient who was at 26th gestational week and the delivery was performed by emergency cesarean upon the detection of fetal bradycardia.[8]

In the study performed, congenital anomaly and fetal loss associated with radiotherapy have not been observed at advanced gestational weeks; however, the increase in childhood leukemia incidence.[10] In our case, the family was informed about the possible risks of radiotherapy and it was decided to postpone treat-

ment to the postpartum period. It was decided to perform the delivery by cesarean at 34th gestational week in accordance with the current literature information[9] and the suggestions of related departments (Obstetrics and Gynecology, Pediatrics, Neurosurgery, Medical Oncology, Radiation Oncology, Anesthesia and Reanimation).

In our case, cesarean was performed under general anesthesia. General anesthesia is preferred in such cases within the literature due to increased intracranial pressure and theoretical increased cerebral trunk herniation risk.[11]

Treatment of brain tumors during pregnancy should be personalized. Surgery is an applicable treatment option in patient group which desire to continue pregnancy. Surgical indication should be decided by considering criteria such as intracranial pathology during diagnosis, gestational week and desire of family. If a small tumor without neurological diagnoses is in question, surgery can be postponed to the end of pregnancy. As in our case, surgical treatment should be applied if any worsening occurs in vital functions. Development of neurological deficits during progress of disease increases the possibility of delivery by cesarean, preterm delivery and support of newborn intense care unit. Radiotherapy treatment can be postponed to postpartum period by informing family (as in our case) only in chosen cases.

## Conclusion

New wide-scale case series are needed to help the management of these rare cases. The treatment should be performed in tertiary centers and by a multidisciplinary approach (Obstetrics and Gynecology, Pediatrics, Neurosurgery, Medical Oncology, Radiation Oncology, Anesthesia and Reanimation) in order to obtain the best obstetric and neurological results.

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# Periodontological Disease of Pregnancy: Pregnant Tumor

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**Abstract**

**Objective:** Our aim was to discuss the treatment and management of pregnant tumor.

**Case:** The pregnant tumor is a periodontological disease similar the benign hyperplastic tumor of gingiva. It is seen in approximately 5 of the pregnants. A 26year old G1P0 patient was admitted to the Mount and Tooth Health Clinic with the complaints of swelling and bleeding in gingiva in the 18th pregnancy week.In oral examination, in the adherent gingiva in the region between right lower 1st and 2nd molar teeth was observed an exsophitic lesion in the diameter of about 4 cm. lesion was removed by the excisional biopsy and the diagnosis of the pyogenic granuloma was established.

**Conclusion:** There is no difference in histopathological features between pregnant tumor and pyogenic granuloma. Elevated hormone levels is one of the most important cause in the etiology. Treatment is generally expectant. Rarely, the surgery is neccessary.

**Keywords:** Pregnancy, pregnancy tumor, piyogenic granuloma.

***Gebeliğin periodondolojik hastalığı: gingivanin hamilelik tümörü***

**Amaç:** Gingivanın hamilelik tümörü tanısı koyduğumuz hastanın tedavi yönetimini vaka üzerinden tartışmaktır.

**Olgu:** Gingivanın hamilelik tümörü, gingivanın selim hiperplastik tümör benzeri periodontolojik bir hastalığıdır. Gebeliklerin yaklaşık 5'inde görülür. 26 yaşında G1P0 hasta 18. gebelik haftasında dişetinde şişlik ve kanama şikâyeti ile Ağız ve Diş Sağlığı Kliniğine başvurdu. Yapılan oral muayenede; sağ alt 1. ve 2. molar dişler arası bölgede yapışık dişetinde yaklaşık 4 cm çapında ekzofitik lezyon görüldü. Lezyon eksizyonel biopsi ile alındı ve piyojenik granülom tanısı konuldu.

**Sonuç:** Piyojenik granülom ile arasında histopatolojik düzeyde bir farklılık yoktur. Etyolojisinde, yükselmiş hormonal düzeyler en önemli nedendir. Tedavisinde nadiren cerrahiye gidilir. Gebelikte asıl yönetim ekspektan yaklaşımdır.

**Anahtar Sözcükler:** Gebelik, gingivanın hamilelik tümörü, pyojenik granülom.

## Introduction

The pregnant tumor which is a periodontological disease, is a lesion resembling the benign hyperplastic tumor of gingiva.[1] Apart from the fact that it occured with the effects of hormonal changes during the pregnancy, in fact its difference in the hystopathological level with pyogenic granuloma observed in males, and the females who are not pregnant,was not demonstrated.[2,3] The greatest difference from pyogenic granuloma is to occur in response to the hormonal changes in pregnancy and to slow down itself within the several weeks after the hormonal changes eliminated together with the end of the pregnancy.[4,5] It is seen in approximately 5% of the pregnants and frequently

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after the first trimester.[6] In its etiology, it has been demonstrated that elevated progesteron levels, local irritants and the bacteria have been effective.[7] Treatment is generally expectant. Rarely, the surgery is neccessary.[6] As the reccurency risk after the surgery performed during the pregnancy is already high, it is not the preferable treatment.[8,9] Under the light of literature, we evaluated a case which we followed up with the pregnancy tumor diagnosis and which we applied the excisional surgery as the bleeding complication developed.

## Case

A 26-year old G1P0 patient was admitted to the Mount and Tooth Health Clinic with the complaints of swelling and bleeding in gingiva in the 18th pregnancy week. In oral examination, exsophitic lesion in the diameter of about 4 cm lying from interdental papilla to vestibular sulcus in the adherent gingiva in the region between right lower 1st and 2nd molar teeth was observed (Figure 1). Oral hygiene training was provided for the patient whose oral hygiene was not in a good condition. Tartars occuring the irritation around the lession were cleaned. Despite this process, lesion kept up with growing in the following two weeks. Spontaneous bleedings were realized to present in the patient expressing that speech and chewing functions were impaired. For this, by applying the oral surgical process to the patient within the 21st pregnancy week, lesion was removed by the excisional biopsy. After the pathological assessment, the diagnosis of the pyogenic granuloma was established. The reccurancy was not detected in the patient observed by the periodical intervals during the pregnancy.

## Discussion

Even if they are the same lesions as pyogenic granulomas in the hystopathological level, the etiology should be established as the definition of pregnancy tumor in the pregnant patients because they have displayed the specific differences as the biological behaviour character and the treatment regimen.[5] This condition is hyperplastic gingivitis and gingival hyperplasy occuring in pregnancy. For this reason, it is also known as the pregnancy gingivitis. It is benign. Its greatest difference from pyogenic granuloma is to be seen in pregnancy and to slow

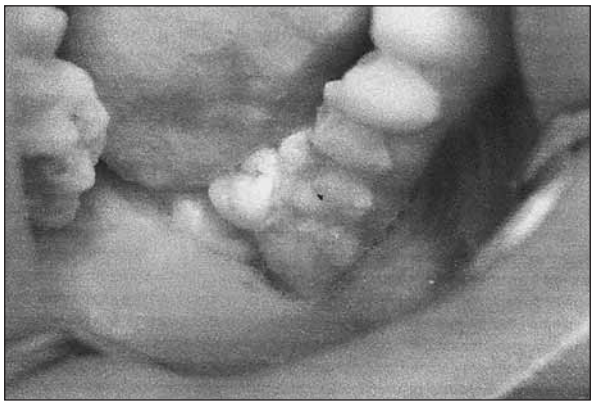

**Figure 1.** A typical pregnancy tumor in view exsophitic lesion in the diameter of about 4 cm lying from interdental papilla to vestibular sulcus in the region between right lower 1st and 2nd molar teeth.

down spontaneusly for a short time as a result of eliminating the hormonal changes after the delivery.[4,5] Even if it may be seen at any age,it is seen in generally young females at the age of reproduction and especially in the ones having bad hygiene. It is observed in approximately 5% of the pregnants and frequently after the first trimester.[6] In its etiology, it was demonstrated that elevated progesteron levels, local irritants and bacteria were effective.[7] In our case, the patient is 26 years old and is in the 18th pregnancy week. As seen in figure 1, the patient's oral hygiene is not in a good condition. It was reported as the pyogenic granuloma as a consequence of pathology examination.

Pyogenic granuloma is a tumor-like reactive inflammatory tissue reaction which occurs depending on the localised trauma and irritation. It is mostly seen in the individuals having bad oral hygiene. Because of the hormonal changes, this disease is seen in females more than the males. In fact, the name of pyogenic granuloma is wrong. Because lesion does not include granuloma and pus. Its surface is generally ulcerative. When peripherical ossified fibrom and peripherical giant cell granuloma occur on gingiva, two lessions are the same clinically as pyogenic granuloma.While pyogenic granuloma may occur in any place of the oral cavity, peripherical ossified fibrom or peripherical giant cell granuloma only occurs on gingiva or alveolar mucosa in oral cavity. Pyogenic granuloma commonly develops on buccal gingiva in interproximal tissue among the teeth. But the diagnosis, clinical picture and the treatment of these three clinical conditions are the same.

While the treatment regimen is scheduled, pregnancy must be in the foreground. In treatment, an expectant attitude is generally followed. But the fact that the lession bleeds and impairs the chewing functions and does not slow down after the pregnancy causes the indications for the surgical approach.[6] As the surgery performed during the pregnancy has a higher reccurency risk, the surgery during the pregnancy is not preferrable treatment aproach.[8,9] But in the conditions which may complicate with the serious bleedings,the treatment method is really difficult in pregnancy. The treatment method in the patient group which the bleeding complication developed is identified by the intensity of the clinical picture. While mouth hygen,locally compression and the drugs stopping the local bleeding may be sufficient in the mild bleedings, the blood transfussion may even be neccessary in the severe bleedings. If the surgery is definitive, the treatment should be stopped within the second trimester of the pregnancy if possible and the patient should be observed in regular intervals.[4] In reccurency or in the group which the surgery can not performed and in the condition which the disease progressed increasingly, the pregnancy is ended that the lung maturation is provided.[10] In our case, the impairments of the patient's speech and chewing functions based on the mass were seen with the progression of the pregnancy week. Subsequently,as the bleedings started, the mass was completely removed by the surgical excision in the 21st pregnancy week. Oral hygiene training was provided for the patient during the pregnancy. And perhaps depending on this, the reccurency was not observed in a long run after the ending and ongoing pregnancy.

In general, prognosis is good. Although it is benign, it is customary for the mass to be removed for both diagnosis and treatment if the long period does not pass following the ending of the pregnancy. Although there is a possibility of reccurency in those which were removed during the pregnancy, there is no generally possibility of reccurency after ending the pregnancy if it is completely removed. And also, oral hygiene should be provided in order to reset the recurrency rate after such treatments. For this, the patient training is definitely essential by the physician. Soft tooth brushes and palatine massage must be definitely recommended.

## Conclusion

Consequently, the fact that pregnancy tumor,one of the diseases of the pregnancy period, having serious complications is known by the gynecologists is invaluable for the attention which should be given by assessing accurately the symptoms related to the mouth health of the patients. The importance of the oral hygiene and the usage of the soft tooth brushes must be taught all pregnants by the jynecologist physicians so that the development of the disease could be prevented rather than provided the treatment and the diagnosis of the disease.

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# Meckel-Gruber Syndrome: A Report of Three Cases

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**Abstract**

**Objective:** We aimed to present three rare cases of MeckelGruber syndrome, the diagnosis of which was made prenatally by ultrasonographic examination of the fetuses.

**Case:** Three pregnancies which were diagnosed prenatally to have occipital encephalocele, postaxial polydactily and bilateral multicystic dysplastic kidney were terminated. In autopsy, they were identified as MeckelGruber syndrome.

**Conclusion:** MeckelGruber syndrome is a rare, lethal, autosomal recessive multisystemic disorder. This syndrome is characterized by central nervous system defects, cystic renal dysplasia, and ductal proliferation in the portal area of the liver and postaxial polydactily. The signs of the syndrome can be detected during the routine ultrasonographic examination between 1114th weeks of the pregnancy. Because of high rate of recurrence risk (25), patients should be closely followed in future pregrancies.

**Keywords:** Fetal anomaly, Meckel Syndrome, prenatal diagnosis.

*Meckel-Gruber Sendromu: üç olgunun sunumu*

**Amaç:** Seyrek görülen üç MeckelGruber Sendromu olgusunu yeni bilgiler ışığında sunmak.

**Olgu:** Prenatal dönemde ensefalosel, bilateral polikistik böbrek ve polidaktili saptanan üç olguda gebelik sonlandırıldı. Otopsi sonucu MeckelGruber Sendromu tanısı kondu.

**Sonuç:** MeckelGruber sendromu otozomal resesif geçiş gösteren letal multisistemik bir hastalıktır. Santral sinir sisteminin gelişimsel anomalileri, kistik displastik böbrekler, hepatobilier duktal plate malformasyonu ve postaksiyal polidaktili gibi bozukluklarla karakterizedir. Gebeliğin 11-14. haftalarında yapılan rutin ultrasonografik tarama ile MKS tanısı konulabilir. 25 tekrarlama riski nedeni ile olgular sonraki gebeliklerinde yakın takip gereklidir.

**Anahtar Sözcükler:** Fetal anomali, Meckel Sendromu, prenatal tanı.

## Introduction

Meckel-Gruber syndrome (MKS) is a lethal, autosomal recessive multi-systemic disorder. Cystic renal dysplasia, and ductal plate malformation characterized by ductal proliferation and fibrosis in the portal area of the liver are classical findings. In fetuses, occipital meningoencephalocele and postaxial polydactily are found by 90% and 80% respectively.[1] From 2005 to September 2010, 233 fetuses were evaluated at Department of Pathology and 3 of these fetuses were diagnosed as MKS.

## Case

All the cases were fetuses with abnormal prenatal findings detected and terminated during the routine ultrasonographic examination.

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Gestational age was between 16 to 18 weeks. In two cases, there was first and in one case third degree consanguinity. There were occipital encephalocele, postaxial polydactily and bilateral multi-cystic dysplastic kidney in the all the cases (Figure 1A, 1B, 2A, 2B). In one case, micrognathia (Figure 1A) and in another one bowing of long tubular bones (Figure 2C) were observed. Kidney and liver findings were similar. In kidney sections of fetuses, cysts of various sizes were found (Figure 3A). A stroma of loose mesenchyme was located between the cystic lesions. The epithelial lining of the cysts wall was cubical or flattened. Primitive glomerular structures were detected in the renal cortex (Figure 3B). In the liver section, fibrosis and proliferation of the bile ducts in the portal area were noted (Figure 3C). In encephalocele sac section, immature neuroglia tissues were detected. Detailed findings are shown in Table 1.

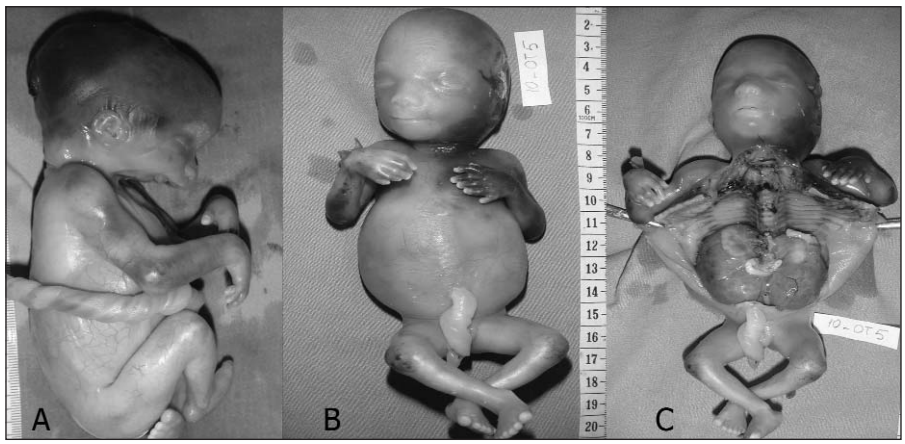


**Figure 1.** **A**; Case 1; Meckel Gruber Syndrome, Polydactyly, micrognathia, encephalocele sac, abdominal distantion. **B**; Case 2; Meckel Gruber Syndrome, Polydactyly, abdominal distantion. **C**; Case 2; Bilateral large, multicyctic kidneys.

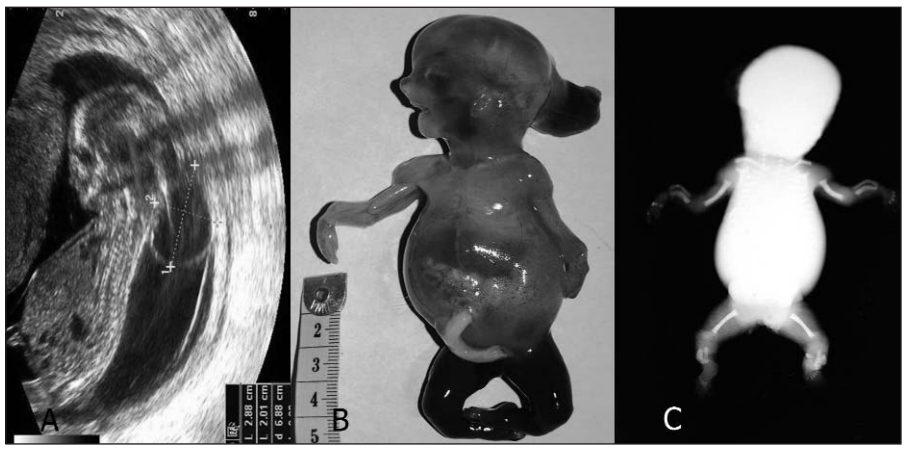


**Figure 2.** **A**; Case 3; Meckel Gruber Syndrome, USG findigs. **B**; Case 3; Polydactyly, abdominal distantion, bowing of long tubular bones. **C**; Case 3; X-Ray findings.

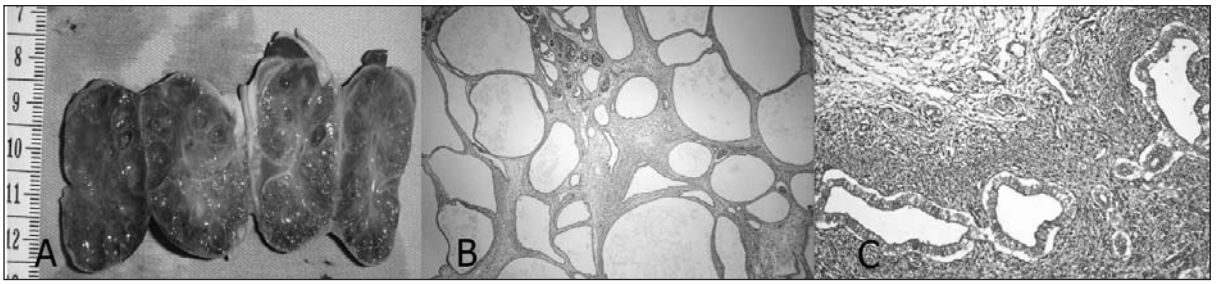


**Figure 3.** **A**; Gross appearance of bilateral multi-cystic dysplastic kidneys. **B**; Microskopic appearance of multi-cystic dysplastic kidneys. **C**; Microskopic appearance of bile duct proliferation and hepatic fibrosis (ductal plate malformation) in the liver.

**Table 1.** Findings about three Meckel-Gruber syndrome cases detected during prenatal period.

| | Age of mother | Consanguinity | Sex of fetus | Prenatal findings | Autopsy findings |
|---|---|---|---|---|---|
| Case 1 | 21 | 3st degree | Male<br>1st pregnancy | 18 week fetus,<br>Bilateral cystic kidney and oligohydramnios | 17 week fetus, Polydactily, micrognathia, bilateral multi-cystic dysplastic kidney, encephalocele, and ductal plate malformation of the liver |
| Case 2 | 26 | 1st degree | Female<br>1st pregnancy | 16 week fetus,<br>Growth retardation,<br>Bilateral cystic kidney and encephalocele | 15 week fetus, Polydactily, bilateral multi-cystic dysplastic kidney, encephalocele, and ductal plate malformation of the liver |
| Case 1 | 29 | 1st degree | Male<br>3rd pregnancy 1 abortion<br>1 alive | 18 week fetus,<br>Bilateral cystic kidney and encephalocele | 18 week fetus, Polydactily, bowing of long tubular bones, bilateral multi-cystic dysplastic kidney, encephalocele, and ductal plate malformation of the liver |

## Discussion

In Meckel-Gruber syndrome, in addition to classical findings, various anomalies have also been reported. These anomalies include such central nervous system as microcephaly, cerebellar hypoplasia, and ventriculomegaly; heart malformations such as patent ductus arteriosus and atrial septal defect; internal and external genital anomalies like ovarian agenesis, bicornuate uterus, and genital ambiguity; urinary system anomalies such as horse-shoe kidney, missing ureters, and hypoplastic urinary bladder; and other anomalies like simian line, shortening and bowing of long tubular bones, cleft lip/palate, papillomatosis and fissure of tongue, atypical face with short nose and low-set ears.[1-5] The findings obtained as regards MKS are presented in Table 2. MKS is precisely diagnosed with the presence of two classical findings or two other anomalies in addition to one classical finding. Classical findings were detected in all of our cases. In the diagnosis of MKS cases, fibrosis and bile duct proliferation in the portal area of the liver are of high importance. Compared to healthy fetus liver, in MKS cases, increased microfibroblastic cells around bile ductules in the portal area were also identified. In experimental animals, fibroblastic cells around bile ducts in the portal area are trans-

**Table 2.** Most frequent manifestations in Meckel-Gruber syndrome.

| | |
|---|---|
| Genitourinary | **Cystic kidney dysplasia** (100%)<br>External/internal genital and ureter anomalies |
| Hepatobiliary | **Bile duct proliferation, hepatic fibrosis and cysts** (ductal plate malformation) (100%) |
| CNS | **Occipital meningo-encephalocele** (90%)<br>Dandy-Walker malformation<br>Arnold-Chiari malformation<br>Agenesis of the corpus callosum<br>Anencephaly<br>Cerebral/cerebellar hypoplasia |
| Skeletal | **Postaxial polydactily** (80%)<br>Shortening and bowing of long tubular bones |
| Other | Heart malformations<br>Cleft lip/palate<br>Micrognathia<br>Microphtalmia |

formed into myofibroblastic cells, causing bile duct ligation. The distribution of the myofibroblastic cells in the tissue remodeling MKS partially resembles that of bile duct ligation or unusual liver damage.[6] The worldwide incidence of the disease varies from 1/140,000 (Great Britain) to 1/3500 (North Africa) in live births.[1] In our province, the average annual birth rate is 29.584.[7] In our 5-year study, 3 MKS cases were diagnosed. The prevalence of MKS in our province is 1/49,300 births. Most of pregnancies with MKS fetuses end with death. It is possible to detect and diagnose MKS by ultrasound examination at 11th to 14th weeks of gestation. In later pregnancies, oligohydramnios might make it increasingly more difficult to establish the diagnosis by ultrasound only.[8] The earliest diagnose was made at 12th gestational week.[9] However there are few cases who lived 7 and 9 months after a term delivery.[4,10] Pregnancies with MKS fetuses may be associated with an elevated maternal serum α-fetoprotein level and an abnormal screening test. In some MKS cases, fetal serum α-fetoprotein levels might increase.[11] MKS show genetic heterogeneity. Recently, many genes have been established to be associated with the formation of MKS. Three of these reported genes are loci, i.e., MKS1 on 17q21-q24, MKS2 on11q13 and MKS3 on 8q24.[1] Whereas MKS1 is identified in Finnish and Caucasian people, MKS2 is found in families from the Middle East and North Africa, and MKS 3 in families from Pakistan and Northern India.[1,12] In a study carried out by Frank et al, 25 MKS cases were evaluated from different countries, including 9 cases from Turkey. MKS1 mutated gene was identified in 4 of the 9 cases from our country, and the other 5 cases were found to have no connection with gene defects.[1] In some studies on genotype-phenotype correlation, compared to MKS1, in MKS3, postaxial polydactily is rarer.[1] MKS1 gene is associated with ciliated function in the cell. Ciliary dysfunction is associated with MKS1.[1] Differential diagnosis for MKS includes Bardet-Biedl syndrome (BBS), trisomy 13, and Smith-Lemli-Opitz syndrome. BBS is characterized by obesity, hypogonadism, learning difficulty, progressive retinal dystrophy, and postaxial polydactily. Renal pathologies are similar in MKS and BBS, but CNS anomalies and proliferation of the bile ducts in the portal area are not observed in BBS.[1,8] In trisomy 13, polycystic kidneys (15-30%), hydronephrosis, horseshoe kidneys, and duplicated ureters can be observed. Trisomy 13 can be diagnosed through central system abnormalities such as holoprosencephaly. In addition, cardiovascular malformations, ocular anomalies, heterotopic pancreatic or splenic tissues, and postaxial polydactily can also be identified, but trisomy 13 does not have hepatic fibrosis. Karyotype analysis is important in differential diagnosis of MKS cases from trisomy 13.[8] In MKS cases, karyotype is normal.[3] In our case, abnormal karyotype was not detected. The final diagnosis was made through autopsy. In differential diagnosis, another pathology to be considered is Smith-Lemli-Opitz syndrome, an autosomal recessive disorder, which is characterized by such central nervous system anomalies as microcephaly, cerebellar hypoplasia, and ventriculomegaly; genito-urinary system anomalies such as genital

ambiguity, hydronephrosis, renal cystic dysplasia, adrenal duplication; and postaxial polydactily of hands but less often of feet. In this syndrome, there are mutations and deficiency of 7-dehydrocholesterol gama-reductase (DHRC7). Hepatic dysfunction and cholestatic liver disease are found in this syndrome.[8]

## Conclusion

MKS has a high risk of recurrence (25%). It is important to examine pregnancies with anomaly fetus histories. For certain diagnosis, autopsy must certainly be done and families should be informed about the possible risks. Early (11-14th weeks) ultrasonographic examination must be suggested for the following pregnancies.

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# Cornelia De Lange Syndrome: A Case Report

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**Abstract**

**Objective:** Cornelia de Lange syndrome (CDL) is a congenital disease characterized by severe mental retardation, pre and postnatal symmetric growth delay, limb defects, visceral defects and a typical dysmorphic face with hirsutism. In our case, a patient with CDL syndrome is presented in the highlights of previous literature.

**Case:** A 31 year old patient, gravida 2, para 1, was referred at 30 weeks of gestation to the perinatology department for assesment of early intrauterine growth retardation (IUGR). The early onset symetrical IUGR was diagnosed on the basis of the fetal biomethric parameters. Mild flexion deformity was also identified. Micrognathia and a 4 mm in size hypoplastic nasal bone were identified with a dysmorphic face pattern.

**Conclusion:** A suspected CDL syndrome must be on mind in cases of early onset symmetrical IUGR with the coexistence of extremity anomalies and dysmorphic facial apperance. Postnatal diagnosis of this syndrome is therefore based on the characteristic clinical phenotype. Similarly, antenatal detection depends on ultrasonographic identification of typical phenotypic features seen in infants with CDL syndrome.Because of the prenatal genetic diagnosis possibility and the recurrence risk for the next pregnancy the prenatal counselling must be given for the suspected cases of CDL syndrome patients.

**Keywords:** Cornelia de Lange syndrome, early onset entrauterine growth retardation, dismorphic face.

*Cornelia de lange sendromu: olgu sunumu*

**Amaç:** Cornelia de Lange (CDL) sendromu, mikrosefali, sinofriz (orta hatta birleşen kaşlar, uzun kirpikler, antevert burun delikleri, uzun filtrum, ince dudaklar gibi karakteristik yüz görünümü bulgularının bulunduğu, gelişme geriliği, mental retardasyon, hirsutizm ve çoklu kongenital anomalilerin eşlik ettiği nadir görülen bir genetik sendromdur. Olgumuzda, CDL sendromu literatür bilgileri ışığında tartışıldı.

**Olgu:** 31 yaşında, G2 P1, 30 haftalık gebe erken intrauterin gelişme kısıtlılığı saptanması üzerine kliniğimize refere edildi. Kliniğimizde yapılan 30. hafta detaylı fetal ultrasonografisinde, fetal biyometrik ölçümlere göre erken simetrik intrauterin gelişme geriliği tespit edildi.Burun kemiği 4 mm olarak normalden kısa (hipoplastik) ölçüldü. Dismorfik yüz görünümü mevcuttu. Mikrognati ve üst ekstremitede fleksiyon deformitesi belirgindi. Detaylı yapılan fetal ultrasonografik muayene ile fetusta genetik bir anomali olabileceğinden şüphelenildi.

**Sonuç:** CDL sendromu, dismorfik yüz görünümü, üst ekstremite defektleri ve erken başlangıçlı simetrik IUGK tespit edilen her vakada ayırıcı tanıda yer almalıdır. Yapılacak detaylı ultrason muayenesi ile diğer anomaliler kolaylıkla saptanabilir. Hastalığın prenatal genetik tanısının mümkün olması ve tekrarlama riskinin bulunması nedeniyle aileye genetik danışma verilmelidir.

**Anahtar Sözcükler:** Cornelia de Lange sendromu, erken başlangıçlı intrauterin gelişme geriliği, dismorfik yüz görünümü.

## Introduction

Cornelia de Lange syndrome (CDL) is a rare genetic syndrome accompanied by mental retardation, hirsutism and multiple congenital anomalies with diagnoses of face characteristics such as microcephaly, synophrys (eyebrows combining on midline), long eyelashes, anteverted nostrils, long philtrum, thin lips etc.[1] CDL syndrome also known as Brachmann de Lange syndrome was first defined in 1933. CDL syndrome mostly

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appears sporadically. The prevalence of the disease varies between 1/10,000 and 1/50,000.[1] The risk of repeating at next pregnancy is 2-5%.[2] The syndrome considered as having multifactorial etiology generally appears sporadically; however its genetic transition can be low penetrated autosomal dominant or recessive.[3] In prenatal diagnosis of CDL syndrome, there are certain face anomalies and fetal growth retardation, hypertrichosis, visceral anomalies, upper extremity defects and serious neurological damage.[4] In an epidemiological study performed on a wide-scale population, CDL syndrome rate was determined as 1/81,000.[5]

In the light of literature, we discussed Cornelia de Lange syndrome case which was suspected in prenatal period and established certain postnatal diagnosis in our presentation.

## Case

Thirty-one years old case at her 30th gestational week with G 2 P 1 was referred to our clinic due to early intrauterine growth retardation (IUGR). At her first pregnancy, 3500 gr girl baby was delivered by cesarean at her 40th gestational week. There were no kin marriage and no known disease in the medical histories of the patient and her husband. At first trimester scanning test, nuchal translucency was measured as 2 mm. However, biochemical marker results could not be reached. Biochemical markers at her 16th gestational week were found as AFP 19.6 IU/ ml (0.81 MoM), HCG 23634 mlU/ml (1.12 MoM), unconjugated estriol 0.756 ng/ ml (0.46 MoM). Biochemical risk calculated for Trisomia 21 was 1/278, the risk calculated for Trisomiy 18 was 1/1124 and the risk calculated for neural tube defect was below 1/10,000. It was learnt that it was decided to maintain the pregnancy without diagnosing as a result of genetic consultation given to the patient by other center.

In detailed fetal examination on 30th gestational week performed in our clinic, fetal abdomen circumference was measured as below -2 standard deviation (SD) and approximate birth weight as below -2 SD. Early symmetric intrauterine growth retardation was detected according to the fetal biometric measurements. Humerus length was found below -3 SD, radius and ulna heights were found below -4 SD at upper extremity measurements. There was a slight flexion deformity. No abnormality was seen in the hand carpal and metacarpal bones. Slight microcephaly and micrognathia were observed. It was observed that nasal root was depressed and nasal bone was shorter than normal (4 mm) and hypoplastic. The face had a dysmorphic view. No pathology at medulla spinalis and cranial structures are observed. Diaphragmatic hernia and pyelectasis could not be detected. There was no distinctive pathology at lower extremities. Four chambers and major vessel outputs were observed at fetal heart examination. There was no distinctive atrial or ventricular septal defect. Pulsatility index (PI) and resistance index (RI) of right uterine artery were found as 0.5 and 0.39, respectively in Doppler examination and no indent was observed. PI was 0.5 and RI was 0.41 in left uterine artery and again there was no indent. The "a" wave was positive in ductus venosus. Amniotic fluid volume was normal.

Required genetic consultation was provided to the patient who had findings such as symmetric IUGR, distinctive upper extremity shortness, hypoplasia of 5th phalanx, micrognathia and hypoplastic nasal bone and prenatal diagnosis was suggested. The patient specified that she did not want to have prenatal diagnostic invasive test (amniocentesis, cordocentesis etc.) and that she decided to maintain the pregnancy. Thereon, the follow-up of the pregnancy was continued at Perinatology Department. In the detailed examination of the patient at her 34th gestational week, approximate delivery weight was 1835 gr (below -2 SD) and symmetric IUGR was continuing. Umbilical artery PI was 1.55 and RI was 0.82.

2520 gr girl baby was delivered by cesarean at her 38th gestational week. Head circumfer-

ence was measured as 30 cm (below -2 SD). First minute Apgar score was 3 and fifth minute Apgar score was 7. Common face, depressed nasal root, long philtrum, anteverted nostrils, micrognathia, microcephaly (Fig. 1), shortness and flexion deformity at upper extremity, simian line at hand, distinctive hypertrichosis at back and femur (Fig. 2) and low birth weight were observed in the newborn examination. At the second examination performed in pediatrics and genetics department, postnatal diagnosis was established as Cornelia De Lange syndrome according to the literature information.

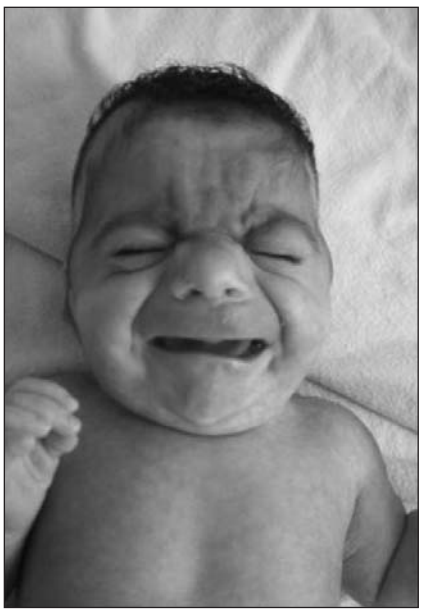

**Figure 1.** CDL syndrome (dysmorphic face view).

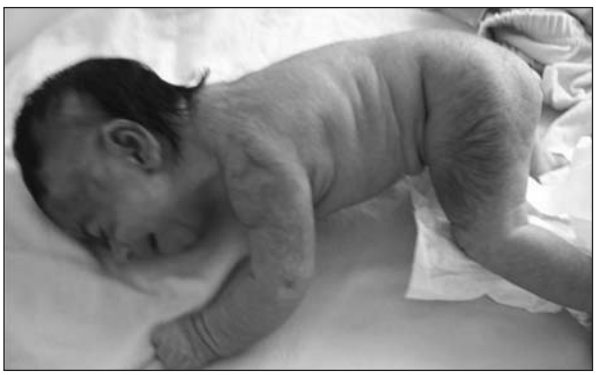

**Figure 2.** CDL syndrome (hypertrichosis).

## Discussion

Cornelia De Lange syndrome is clinically well defined syndrome though it is rare, and it is observed in all cases with dysmorphic face characterized by growth and development retardation, microcephaly, synophrys, long curved eyelashes, downward looking thin lips, long philtrum.1,4,6 3 q 26. 3 chromosomal defect are seen in cases with defined familial history and kin marriage where etiology of syndrome is not known well.[2,7] In sporadic and familial cases, mutation was defined on NIPBL (Nipped – B – like) with cohesin regulator on 5th chromosome.[7,8] Also mutations were detected in SMAC 1A gene on X chromosome and SMC 3 gene on 10th chromosome which are the structural components of cohesin complex. Last two gene defects are related with slighter forms.[9,10] In our case, kin marriage and familial history was not detected. Chromosome analysis performed on the patient and her husband was normal; however mutation analysis was not performed.

In the literature, 15 studies were examined which were diagnosed as CDL syndrome in pre- and postnatal period.[11-24] According to the data of these studies, 95% of patients had IUGR, 81% of them had skeletal anomalies, 50% of them had facial dysmorphism and 50% of them had fetal diaphragmatic hernia. There was polyhydramniosis in two cases and there was increase in nuchal thickness in four cases. Prenatal diagnosis could only be established on six cases (Table 1).[16-19]

Early symmetric IUGR at prenatal diagnosis is the most evident ultrasonographic finding and becomes evident in between 20th and 25th gestational weeks. In our case, early symmetric IUGR was also detected as the most evident pathological finding. The reason that the patient was referred to our clinic was the early beginning IUGR. In IUGR etiology, there are many factors varying according to IUGR type. Intrauterine infections, genetic factors, maternal diseases, malnutrition, drugs, radiation, multiple pregnancies and uteroplacental factors are

among these factors. In our case, it was considered that symmetric IUGR developed according to genetic factor.

While there are several skeletal anomalies, the most significant findings are the defects evident at upper extremity.[25,26] Classical extremity anomalies are micromelia, oligodactylia and terminal transverse hemimelia.

In our case, humerus and radius lengths were measured as below -3 SD. At the same time, there was a slight flexion deformity in upper extremity. Hypoplasia of 5th phalanx and 1st metacarpal bone was seen in 90% of cases in the literature.[25] In our case, no pathology was detected in metacarpal bones except 5th phalanx hypoplasia.

Among facial anomalies, long eyelashes, anteverted nostrils, long philtrum, micrognathia, low ear (dysmorphic face) are the diagnoses that can be observed in prenatal period.[15-19] In our case, micrognathia and hypoplastic nasal bone among facial anomalies were detected in prenatal period (Table 1).

The existence of hypertrichosis is also one of the findings helping to diagnose. The existence of long eyelashes together with hypertrichosis is typical for CDL syndrome (Fig. 2).[19]

Bilateral diaphragmatic hernia, single umbilical artery and unilateral pyelectasis are seen in some cases.[12-15,23] These pathological findings were not observed in our case.

Congenital cardiac anomalies may accompany the syndrome less frequently. These anomalies are ventricular septal defect (VSD), atrial septal defect (ASD), aortic or pulmonary stenosis, Fallot tetralogy, single ventricle, atrioventricular septal defect and aortopulmonary window.[11,13,17] In our case, no cardiac anomaly with prenatal diagnosis was detected.

Less frequently, nuchal cystic hygroma and increased nuchal thickness were seen in some cases.[11,22,24] At first trimester scanning of our case, nuchal thickness was measured as 2 mm.

Another finding helping to diagnose is alpha feto protein (AFP) value below 0.4 MoM measured at 15th gestational week.[11] In our case, AFP value was 0.81 MoM at her 16th gestational week. Findings guiding prenatal diagnosis of CDL syndrome are increased nuchal thickness at first trimester, early beginning symmetric IUGR, evident defects especially at upper extremities and dysmorphic face.[20,23,24,27] Due to non-specific prenatal ultrasonographic diagnoses, the diagnosis can be established after delivery in many cases as in our case. Apert syndrome, Trisomia 18, Fanconi anemia, Holt-Oram syndrome, Multiple pterygium syndrome, Roberts syndrome, Smith-Lemli-Opitz

**Table 1.** CDL syndrome cases with prenatal diagnosis.

| | Goolsby et al[16] | Manouvrier et al.[17] | Ackerman and Gilbert-Barness[18] | Ranzini et al.[19] | Boog et al.[20] | Urban and Hartung[21] | Our case |
|---|---|---|---|---|---|---|---|
| Gestational week | 18 | 33 | 20 | 34 | 20 | 22 | Postnatal diagnosis established |
| IUGR | + | + | + | + | + | - | + |
| Microcephaly | - | - | + | + | + | - | + |
| Extremity defects | + | + | micromelia | + | + | + | + |
| Congenital heart diseases | - | - | - | - | - | - | - |
| Diaphragmatic hernia | + | - | + (bilateral) | - | - | - | - |
| Abnormal face | + | + | + | + | + | + | + |
| Other anomalies | | | | Single umbilical artery, Dandy-Walker variant, unilateral renal pyelectasis, polyhydramniosis | | Cleft palate cerebellar vermis hypoplasia | Hypoplasia of 5th phalanx |

syndrome, thrombocytopenia and absent radius syndrome (TAR) should be brought to mind in prenatal differential diagnosis of CDL syndrome.

## Conclusion

CDL syndrome should be within differential diagnosis in each case where dysmorphic face, upper extremity defects and early beginning symmetric IUGR are detected. Other anomalies can be detected easily by performing a detailed ultrasonographic examination. Genetic consultation should be provided to family since it is possible to establish prenatal genetic diagnosis of disease and there a risk for recurrence.

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