

Evaluation of the Results of Cordocentesis: 9 Years of Experience

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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 umbilical 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 başarıları %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 ulaşamadı. 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 laboratuvar kültür koşulları sağlandığında yüksek güvenilirliği olan invaziv bir tanısal ve tedavisel girişimdir.

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

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 pregnant 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 fetomaternal transfusion may be seen in cordocentesis interventions.⁴

Some factors such as experience of physician performing cordocentesis practice, ultrasonographic 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, abortion 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 pregnant 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% povidone 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 pregnant 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 pregnant 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.

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 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

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 Daffos¹¹ 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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