대한진단검사의학회지 제28권 제5호 2008
Korean J Lab Med 2008;28:378-85
DOI 10.3343/kjlm.2008.28.5.378

임신중기 양수천자 31,615예에 대한 임상 및 세포유전학적 결과

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Clinical and Cytogenetic Findings on 31,615 Mid-trimester Amniocenteses

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Background : Since amniocentesis made prenatal diagnosis feasible in 1967, the method has become a popular tool in obstetric practices. In Korea, the demand for genetic counseling and prenatal tests has increased markedly because the number and proportion of pregnancies in women aged 35 yr and older have increased over a 20-yr period. Here we report clinical and cytogenetic findings on 31,615 mid-trimester amniocenteses.

Methods : To investigate the changes in the annual number of amniocentesis, distribution of indications and age, and cytogenetic findings and abnormality rate according to indications, this study retrospectively analyzed 31,615 cases of mid-trimester amniocentesis performed at Seoul Clinical Laboratories, an independent medical laboratory center, during the past 13 yr (1994-2007).

Results : The annual number of amniocenteses has increased substantially since 1994. Among the 31,615 amniocentesis cases, the maternal age between 30 and 34 yr was the most common age group (35.4%). Among clinical indications, abnormal maternal serum screening results have been the most common indication for amniocentesis since 1994. Chromosomal abnormalities were detected in 973 cases (3.1%). Down syndrome was the most common abnormality found (36.9%, 359/973). In sex chromosomal abnormalities, 53 cases of Turner syndromes, 32 cases of Klinefelter syndromes, 20 cases of triple X syndromes, and 15 cases of 47,XYY were diagnosed. Of structural rearrangements, reciprocal translocations between two autosomes were the most common (15.5%, 151/973). Abnormal ultrasonographic findings showed the highest positive predictive value (5.9%) among the clinical indications.

Conclusions : The present study could be used for the establishment of a database for genetic counseling. The discovery of an abnormality provides the option of termination or continuation in the pregnancy, a more suitable obstetric management in Korea. *(Korean J Lab Med 2008;28:378-85)*

Key Words : *Prenatal diagnosis, Amniocentesis, Chromosomal abnormalities, Genetic counseling*

접 수 : 2008년 1월 22일 **접수번호 :** KJLM2112
수정본접수 : 2008년 3월 21일
게재승인일 : 2008년 3월 22일
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INTRODUCTION

Prenatal diagnosis with cytogenetic analysis has been recognized for more than 20 yr as a safe and reliable method for couples at increased risk of giving birth to a child with a clinically significant chromosomal abnormality[1, 2]. Until

the early 1990s, amniocentesis was performed on patients at an advanced maternal age and on those with an adverse obstetric history. Nowadays, the importance of amniocentesis has been emphasized due to advances in screening using maternal serum markers and ultrasonography, increased awareness of anomalous children affected by environmental pollution, and increasing maternal age. Rates of chromosomal abnormalities have been estimated in live births[3], but increasingly, the data collected during amniocentesis have provided estimates for the pregnancy's second trimester[4, 5], which can be used in genetic counseling. In Korea, the demand for genetic counseling and prenatal tests has increased markedly because the number and proportion of pregnancies in women aged 35 yr and older has increased over a 20-yr period. No extensive data gathered in a single major study is available for indications other than advanced maternal age (AMA) or for other chromosomal disorders, such as structural rearrangements, marker chromosomes or mosaicism. Here we retrospectively analyzed 31,615 cases of mid-trimester amniocenteses referred from various medical sites during the past 13 yr (1994-2007).

MATERIALS AND METHODS

Clinical data were obtained from records at the request of the cytogenetic laboratory, and covered all karyotype analyses of fetal cells from second trimester amniotic fluid between 1994 and 2007 in Seoul Clinical Laborotories, one of the independent medical laboratories in Seoul. The indications of amniocentesis for prenatal diagnosis with cytogenetic analysis include 1) AMA, that is, if the mother is ≥35 yr old at the expected date of confinement; 2) previous history of fetus/child with chromosomal abnormalities or congenital anomalies; 3) family history of chromosomal abnormalities or congenital anomalies; 4) carrier of X-linked recessive disorders; 5) abnormal screening markers (α-fetoprotein, human chorionic gonadotropin, and/or unsaturated estriol) in maternal serum; 6) abnormal ultrasonographic (US) findings; 7) history of missed or recurrent abortions and/or unexplained death in utero; 8) patient anxiety; and 9) twin pregnancies. Abnormal ultrasonographic findings were categorized as follows: fetal and placental malformations (single or multiple), abnormal amniotic fluid volume (polyhydramnios or oligohydrmanios), and intrauterine growth restriction. The distribution of fetal malformations comprised heart anomalies, diaphragmatic hernia, duodenal atresia, abdominal wall defects, fetal effusion/hydrops, hydrocephalus, mild ventriculomegaly, and thickened nuchal fold (>6 mm).

The amniocytes were cultured in three different flasks (in three Petri dishes after the year 2000) containing 2 mL of BIOAMF (Biological, Inc., Kibbutz Beit Haemek, Israel) as the basal medium supplemented with BIOAMF supplement (Biological, Inc.), 1% 200 mM L-glutamine (Gibco, New York, USA), 100 U/mL penicillin (Biological, Inc.), and 100 μg/mL streptomycin (Biological, Inc.) using the technique described elsewhere[6]. Cultures were harvested when colonies were sufficient (at least 15 colonies), 9-15 days (in case of *in situ* culture method, 6-10 days) after seeding. Chromosomes were prepared in the usual manner[6]. Routine diagnosis was performed using the GTG-banding technique[7]. In some cases, analysis was completed by the C-banding technique.

All chromosomal abnormalities detected by karyotype analysis have been classified into the following categories: 1) numerical and structural abnormalities, 2) autosomal and sex chromosomal abnormalities, and 3) balanced and unbalanced structural rearrangements. However, normal variations in chromosomal structures, such as pericentric inversion of chromosome 9, enlarged heterochromatin on various chromosomes, enlarged satellites, and so on, were excluded. Frequencies of observed chromosomal abnormalities were then calculated by indications.

RESULTS

1. Annual number of amniocenteses

The number of amniocenteses requested increased substantially after 1994, particularly sharply in 2000 (Fig. 1).

2. Age distribution

Of the 31,615 amniocenteses, 35.4% (11,192) had a maternal age between 30 and 34 yr, which was the most common age group, followed by age 35–39 (30.1%, 9,516), 25–29 (24.1%, 7,619), older than 40 (7.8%, 2,466), 20–24 (2.5%, 790), and 19 yr or younger (0.1%, 32) (Table 1). According to the annual distribution of maternal age groups, the groups aged 30–34 and 35–39 gradually increased, and the groups aged 20–24 and 25–29 decreased, since 1996 (Fig. 2).

3. Clinical indications

The most common clinical indication for amniocentesis was abnormal maternal serum screening results (69.5%), followed by AMA (18.4%), abnormal US findings (5.7%), previous chromosomal abnormalities (1.3%), and previous neonatal death or stillbirth (1.2%) (Table 2). Since 1994, abnormal maternal serum screening results have been the most common indication for amniocentesis, followed by AMA and abnormal US findings (Fig. 3). According to the distribution of maternal age groups by clinical indications, AMA was the most common indication in ages 35–39, and abnormal maternal serum screening results were the most common indication in ages 30–34, followed by ages 35–39 (data not shown).

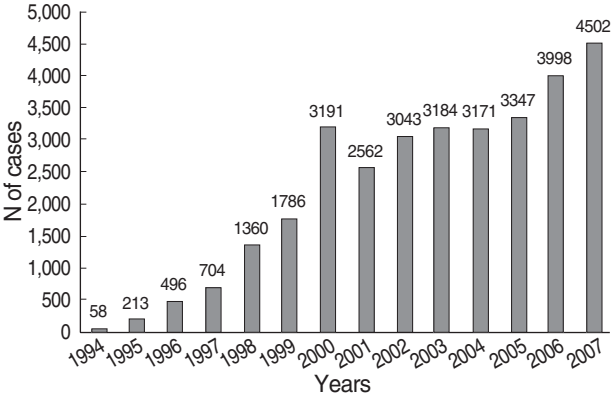

Fig. 1. Annual distribution of amniocentesis cases in Seoul Clinical Laboratories, Seoul, Korea.

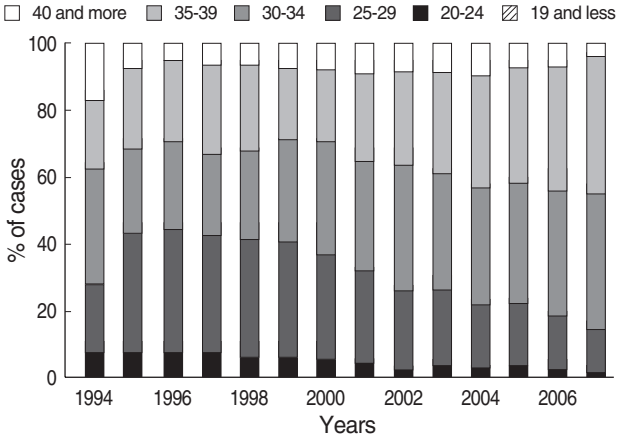

Fig. 2. Annual distribution of maternal age group.

4. Cytogenetic findings

Of the 31,615 amniocenteses, 30,642 cases (96.9%) showed normal diploidy and 973 cases (3.1%) showed chromosomal abnormalities. Among these chromosomal abnormalities, numerical and structural abnormalities were seen in 595 and 378 cases, respectively. The majority of chromosomal abnormalities were autosomal trisomies (48.8%, 475/973). Down syndrome was the most common abnormality (36.9%, 359/973). Among the 359 Down syndrome cases, classic (or

Table 1. Age distribution

Maternal age (yr)	N of patients	%
-19	32	0.1
20-24	790	2.5
25-29	7,619	24.1
30-34	11,192	35.4
35-39	9,516	30.1
40-	2,466	7.8
Total	31,615	100.0

Table 2. Clinical indications of prenatal genetic amniocentesis

Indications	N of cases	%
Advanced maternal age (>35 yr)	5,817	18.4
Previous chromosomal abnormalities	411	1.3
Previous congenital anomalies	348	1.1
Family history of chromosomal abnormalities	190	0.6
Family history of congenital anomalies	63	0.2
Carrier of X-linked recessive disorder	32	0.1
Abnormal maternal serum screenings results	21,972	69.5
Abnormal ultrasonographic finding	1,802	5.7
Previous neonatal death or stillbirth	379	1.2
Patient anxiety	348	1.1
Twin pregnancy	253	0.8
Total	31,615	100.0

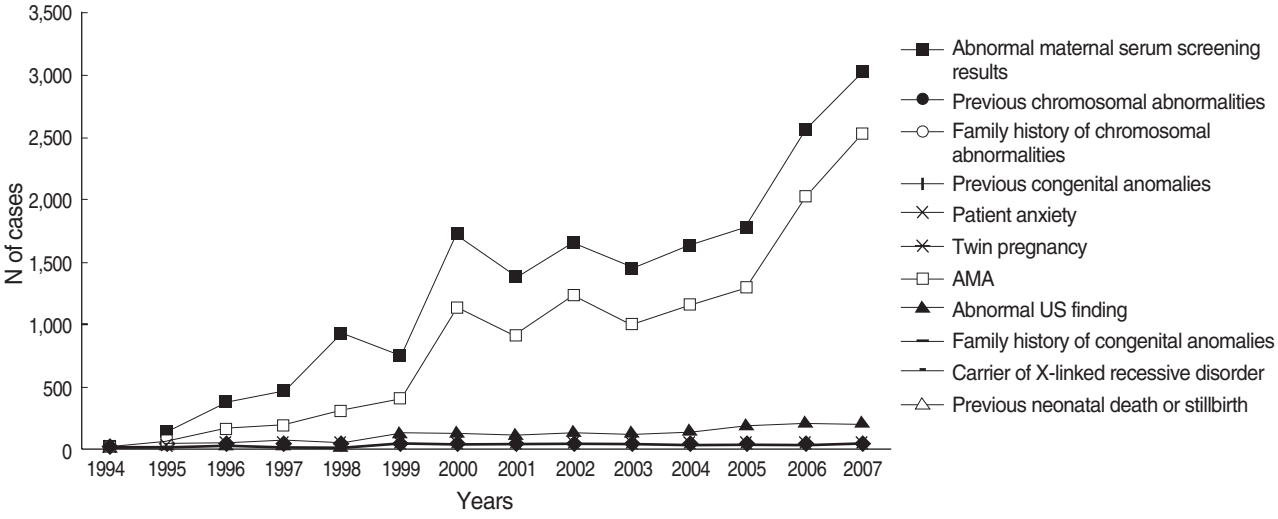

Fig. 3. Annual distribution of amniocentesis cases by clinical indications.

standard) Down syndrome, mosaicism, and Robertsonian translocation accounted for 88.9% (319/359), 2.5% (9/359), and 8.6% (31/359), respectively. Edward syndrome and Patau syndrome, including mosaicism, were found in 99 and 12 cases, respectively. The prevalence of Down syndrome cases increased by an annual rate of 0.1% from 1994 to 2007. In cases with sex chromosomal abnormalities (120 cases), 53 Turner syndromes, 32 Klinefelter syndromes, 20 triple X syndromes, and 15 47,XYY were observed. Among the 53 Turner syndromes, standard monosomy, mosaicism, and structural rearrangement (isochromosome of Xq10 and deletion of Xp or Xq) accounted for 34.0% (18/53), 54.7% (29/53), and 11.3% (6/53), respectively. The classifications for each of the autosomal trisomies and sex chromosomal abnormalities are shown in Table 3. Total structural rearrangements were found in 378 cases (38.8%, 378/973). Balanced structural rearrangements were found in 258 cases, of which reciprocal translocations between two autosomes were much more common (151 cases) than between sex chromosome and autosome (8 cases). Among the 159 reciprocal translocations, 130 cases were parentally inherited and 29 originated *de novo*. Unbalanced structural rearrangements were found in 120 cases, of which supernumerary marker chromosomes (SMCs) were observed most commonly (31 cases), followed by deletions (26 cases) and duplications (16 cases). Among the 31 marker chromosomes, 20 were parentally inherited and 11 originated *de novo*. Other frequencies by classification for chromosomal abnormalities are shown in Table 3.

5. Frequency of chromosomal abnormalities by indications

Of the 1,802 cases with abnormal US findings, 106 resulted in chromosomal abnormalities, which showed the highest positive predictive value (5.9%) among indications, followed by previous chromosomal abnormalities (4.9%), previous congenital anomaly (4.0%), family history of chromosomal abnormalities (3.7%), AMA (3.4%), and abnormal maternal serum screening results (2.8%) (Table 4).

DISCUSSION

Since prenatal diagnosis by chromosomal analysis became available using amniocentesis in 1967, it has been increasingly used in obstetric practices for the diagnosis and treatment between 15 and 18 gestational weeks. In the 1980s amniocentesis was used primarily for those in advanced maternal age groups, at least 35 yr old. So far, other recent reports have still shown that prenatal diagnosis of chromosomal disorders has been performed mainly for pregnancies at an advanced maternal age[8, 9]. This study found

Table 3. Frequencies of chromosomal abnormalities

Karyotypes	N	%
Numerical abnormalities	595	61.2
Autosome	475	48.8
Trisomy 21	359	36.9
Classic	319	
Mosaicism	9	
Translocation	31	
Trisomy 18	99	10.2
Classic	96	
Mosaicism	3	
Trisomy 13	12	1.2
Classic	8	
Mosaicism	1	
Translocation	3	
Trisomy 20	4	0.4
Trisomy 8	1	0.1
Sex chromosome	120	12.3
Turner syndrome	53	5.4
Classic	18	
Mosaicism*	29	
Structural rearrangment†	6	
Klinefelter syndrome	32	3.3
Classic	27	
Mosaicism	5	
Triple X syndrome	20	2.1
47,XYY	15	1.5
Structural rearrangements	378	38.8
Balanced	258	26.5
Reciprocal translocation	159	16.3
Autosome-Autosome	151	
Sex chromosome-Autosome	8	
Robertsonian translocation	54	5.5
Inversion	45	4.6
Unbalanced	120	12.3
Supernumerary marker chromosome	31	
Deletion	26	
Duplication	16	
Addition	15	
Complex rearragement	13	
Dicentric chromosome	7	
Isochromosome	7	
Ring chromosome	4	
Insertion	1	
Total	973	100.0

*45,X/46,XX; 22cases, 45,X/46,XY; 5 cases, 45,X/47,XYY; 2 cases, †isochromosome of Xq10; 4 cases, deletion of Xp or Xq; 2 cases.

that abnormal maternal serum screening has been the most common indication for amniocentesis since 1994, followed by advanced maternal age (Table 2, Fig. 3). This finding was similar to the results of previous studies in Korea[10–15]. Among the maternal age groups, abnormal maternal serum screening results were the most common indication in patients aged 30 to 34. Maternal serum screening test has been accepted as the prominent indication for amniocenetesis among the obstericians over time. In particular, this test has made remarkable progress as both a routine prenatal screening program and a detection technique in Korea. In cases with a previous birth that displayed, or a family history of, congenital anomalies or chromosomal abnormalities, there should be a proper diagnosis in consideration of psychiatric stress which could affect the family. This study found 1,012 amniocenteses (3.2%) were requested due to the previous or family history of chromosomal abnormalities or congenital anomalies.

Table 4. Frequencies of chromosome abnormalities according to the indications

Indications	Chromosome abnormalities		
	Total	N	%
Advanced maternal age (≥35 yr)	5,817	196	3.4
Previous chromosomal abnormalities	411	20	4.9
Previous congenital anomalies	348	14	4.0
Family history of chromosomal abnormalities	190	7	3.7
Family history of congenital anomalies	63	0	0.0
Carrier of X-linked recessive disorder	32	0	0.0
Previous neonatal death or stillbirth	379	9	2.4
Abnormal maternal serum screening	21,972	615	2.8
Abnormal ultrasonographic finding	1,802	106	5.9
Patient anxiety	348	2	0.6
Twin	253	4	1.6
Total	31,615	973	3.1

The reports on prenatal diagnosis of amniocentesis, consisting of various numbers of cases, have revealed that the incidence of chromosomal abnormalities ranges between 1.0% and 6.7%[8, 10–17]. This study found that 3.1% of 31,615 cases had chromosomal abnormalities, which was similar to the data of Karaoguz et al. (3.0%)[8] and Tseng et al. (2.9%)[9]. A number of cases varies in many studies but, to our knowledge, this study constitutes the largest report in Korea. Down syndrome was the most common abnormality found (36.9%, 359/973). Among the 359 Down syndrome cases, classic (or standard) Down syndrome, mosaicism, and Robertsonian translocation cases accounted for 88.9% (319 cases), 2.5% (9 cases), and 8.6% (31 cases), respectively. Of these values, classic Down syndrome showed a lower, and Robertsonian translocation type showed a higher incidence than those seen in previous studies[18–20]. This find-

ing might represent the different proportion of cytogenetic forms of Down syndrome in Korea. The present study found that the annual prevalence of Down syndrome cases has slowly increased since 1994, which might be due to an increase in a number of pregnancies in the advanced maternal age group (Fig. 2), and to a remarkable progress in the maternal serum screening test and ultrasonographic techniques. Of the sex chromosomal abnormalities, Turner syndrome was the most common (0.2%, 53/31,615). Among the 53 Turner syndrome cases, standard monosomy, mosaicism, and structural rearrangement accounted for 34.0% (18 cases), 54.7% (29 cases) and 11.3% (six cases), respectively. Compared to the relative frequencies of Turner syndrome reported by Jacobs et al.[21] and Sybert[22], standard monosomy and structural rearrangement were found in this study at a lower, and mosaicism at a higher, incidence, which might be due to the possibility of maternal cell contamination and the high sensitivity of detecting mosaicism by the in situ culture method. But other reports have found that mosaicism is common in Turner syndrome, ranging from 66.7%[23] to 90% of cases[24]. The prognosis for mosaic cases is different from pure X monosomy, and the identification of low level mosaicism is crucial for providing accurate prenatal counseling to parents[25]. In this study, some of the mosaic cases showed a second cell line containing two normal X chromosomes (22 cases, 41.5%). Others showed a second cell line containing a Y chromosome (46,XY or 47,XYY), which was found in 13.2% of Turner syndrome cases, which is similar to the study of Gravholt et al. (12.2 %)[26]. In the study of Huang et al.[27], 9.5% of Turner syndrome cases were identified as having a Y chromosome. Although the phenotype 45,X/46,XX varies from normal female to full manifestations of Turner syndrome, it has been reported that the abnormal phenotypic rate of prenatally diagnosed cases is about 14% at birth[28]. Furthermore, because the presence of a Y chromosome or Y chromosome sequences can be associated with a risk of developing neoplasia of the gonad (gonadobalstoma or dysgerminoma), or virilization and a wrong fetal sex assessment, molecular testing for the sex determining region on Y (SRY) gene should also be performed both during prenatal diagnosis and after birth[26, 27]. Among the 378 structural rearrangements, balanced reciprocal translocations (159 cases) were the most common. Unbalanced structural rearrangements (12.3%, 120/973) were detected as frequently as sex chromosome abnormalities. Among these 120 unbalanced structural rearrangements, SMCs were the most common (31 cases). Among these 31 SMCs, 20 cases were familiar nine cases were *de novo*, and the origin was undetermined in two cases. FISH (or other molecular techniques) is important for establishing acrocentric or nonacrocentric chromosomes in the origin of SMCs. Reports from Crolla [29] and Huang et al.[30] indicate an overall low risk of acrocentric SMCs, and a higher risk of nonacrocentric SMCs.

In studies by Yang et al.[31], Tseng et al.[9], and Karaoguz et al.[8], abnormal US findings showed the highest detection rate for chromosomal abnormalities in prenatal diagnosis, at 6.5%, 8.9%, and 5.3%, respectively. In the present study, of the 1,802 cases with abnormal US findings, 106 cases resulted in chromosomal abnormalities, which showed the highest positive predictive value (5.9%) among the indications. Nowadays, highly sensitive ultrasonic technology can detect many fetal anomalies which eventually necessitate amniocentesis.

In summary, the incidence of mid-trimester genetic amniocentesis as a prenatal diagnostic test for Korean women has increased substantially since 1994. Until the early 1990s, prenatal diagnosis by amniocentesis was performed mainly for advanced maternal age. However, due to the development of maternal serum markers and sensitive ultrasonic technology, the indications for amniocentesis are changing in Korea. Of the 31,615 cases, 973 (3.1%) cases showed chromosomal abnormalities, the most common of which was Down syndrome. The cytogenetic forms of Down syndrome and Turner syndrome appeared in proportions different from those seen in previous studies. However, further studies by more investigators are required to verify this finding.

Generally, people who decide to perform amniocenteses for prenatal diagnosis are concerned about specific chromosomal conditions, the most common of which is Down syndrome. However, unexpected abnormalities are more

likely than the "expected" ones. Our data could offer a database for proper prenatal genetic counseling of pregnant women and their spouses/partners, and for future pregnancies in Korea.

요 약

배경 : 1967년 처음 양수천자에 의한 산전진단이 가능하게 된 이래 산부인과에서 산전진단을 위한 방법으로 양수천자가 널리 이용되고 있다. 국내에서는 특히 지난 20년간 35세 이상의 노령 산모의 비율이 증가되고 있어 산전진단과 유전상담에 대한 요구가 높아지고 있다. 이에 저자들은 본 검사실에 의뢰되었던 임신중기 양수천자 31,615예에 대한 임상 및 세포유전학적 결과에 대해 분석하였다.

방법 : 1994년부터 2007년까지 13년 동안 전문검사수탁의료기관인 서울임상검사센터에서 임신중기 양수천자 31,615예를 대상으로 연도별 양수검사건수의 변화, 검사대상자의 연령 및 임상적응증의 분포, 염색체 핵형 결과와 임상적응증에 따른 염색체이상의 발생빈도에 대해 후향적으로 분석하였다.

결과 : 양수검사 의뢰건수는 1994년도 이래 점진적인 증가를 보였다. 산모들의 연령분포를 보면 30에서 34세 사이의 연령군이 35.4%로 가장 높은 빈도를 보였으며 임상적응증의 분포에서는 모체혈청 표지자의 선별검사상 비정상소견을 보인 경우가 1994년도 이래 가장 높은 빈도를 나타냈다. 염색체 핵형 분석결과는 비정상핵형이 973예로 3.1%이었는데 그 중 다운증후군이 비정상핵형 973예 중 359예(36.9%)에서 관찰되어 가장 높은 빈도를 나타냈다. 성염색체 이상 중에는 터너증후군 53예, 클라인펠터증후군 32예, 트리플 X 증후군 20예, 47,XXY 15예로 관찰되었다. 구조적 이상 중에는 상염색체 간의 균형 재배열이 151예, 15.1%에서 관찰되어 가장 높은 빈도를 나타내었다. 임상적 응증들 중 비정상적인 초음파 소견을 보인 경우가 염색체 이상에 대한 가장 높은 양성 예측률을 보였다(5.9%).

결론 : 본 연구결과는 국내의 산모들에 대한 산전유전상담을 위한 기초자료가 될 것이며 특히, 염색체 이상에 대한 결과는 실제 임상에서 임신유지 여부를 판단하는 데 도움이 될 것으로 생각된다.

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