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The Korean Collaborative Study on 11,000 Prenatal Genetic Amniocentesis

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Abstract

Since amniocentesis made prenatal diagnosis feasible in 1967, the method has been remarkably instrumental in obstetrical practice. A recent study conducted between 1980 and 1997 collected 11,000 amniocentesis procedures done at 10 university hospitals and tertiary centers in Korea. The study indicated that the use of amniocentesis on patients has increased steadily since 1980; however, the number has increased sharply for patients in the mid 1990's. In the 1980's, amniocentesis had been used primarily for patients in advanced maternal age groups (at least 35 years or older). In 1995, amniocentesis had been implemented for the detection of abnormal serum markers (37.6%), and by 1997, amniocentesis was involved in such diagnosis even more frequently (44.8%). Of the total number of uses, 270 (2.5%) involved the detection of chromosomal anomaly. In autosomal disorders, 96 Down syndrome, 33 Edward syndrome, and 6 Patau syndrome were diagnosed. In sex chromosomal anomaly, 10 Turner syndrome, and 10 Klinefelter syndrome were diagnosed. Added to that, 83 translocations, and 15 mosaicisms were diagnosed. Of the 322 cases with abnormal ultrasonographic findings, 21 (6.5%) resulted in chromosomal anomaly. The use of genetic amniocentesis as a prenatal diagnostic test for Korean women has risen 10-fold between 1988 and 1998. As stated earlier, amniocentesis had earlier been used primarily for those in advanced maternal age groups. Today, maternal serum markers and highly sensitive ultrasonic technology can detect many fetal anomalies which eventually necessitate amniocentesis.

Key Words: Amniocentesis, chromosomal abnormality, indication, prenatal diagnosis

INTRODUCTION

Schatz introduced amniocentesis for the treatment of hydramnios in 1882,[1] and it was also used for the diagnosis and treatment of Rhesus incompatibility. Fuchs and Riis reported the use of amniocentesis in sex determination in 1956.[2] Chromosomal analysis using a cell culture obtained by amniocentesis was reported by Steele and Bregs in 1966, and since 1967 prenatal diagnosis using amniocentesis has been in use.[3,4] Amniocentesis is currently the most commonly used invasive prenatal diagnostic method. It is done between 15 and 18 gestational weeks. Almost all of the cell cultures succeed; therefore it can be used for the diagnosis of chromosomal anomalies as well as carriers of genetic diseases using DNA and enzyme analysis. In the early days, amniocentesis was applied to patients of advanced maternal age and those with previously adverse obstetric history. Nowadays, the importance of amniocentesis has been highlighted due to advances in screening using maternal serum markers and ultrasonography, increased awareness of anomalous children affected by environmental pollution, and increasing maternal age. Consequently, changes in the incidence, patient age, and indications of amniocentesis can be postulated, but no analytical report has been cited so far. Accordingly, this collaborative study analyzed 11,000 amniocentesis procedures performed at 10 university hospitals as well as tertiary centers in Korea from 1980 to 1997. The changes in annual incidence, maternal age distribu-

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tion, indications, cytogenetic results, as well as the relationship between indications and the incidence of chromosomal anomalies were analyzed.

MATERIALS AND METHODS

In this study, 11,000 amniocentesis procedures performed from 1980 to 1997 in Korea were analyzed. The participating centers included the colleges of medicine at Yonsei, Koryo, Kyunghee, Hanyang, Ajou, Pusan, Keimyung, Pochun CHA and Sungkyunkwan Universities as well as Pusan Ilsin Christian hospital.

After complete voiding, ultrasonographic examination was done for the confirmation of gestational week, placental location, and amniotic fluid volume of the patient. Under ultrasonographic guidance, the insertion angle and direction of the needle was determined at the best point where fluent amniotic fluid and limbs of the fetus are observed, avoiding the placenta and umbilical cord. The abdomen was draped and local anesthesia with 2% lidocaine was applied. Using the 22 G spinal needle, 20−30 ml of amniotic fluid was aseptically obtained and immediately sent to the lab. After centrifugation of the obtained amniotic fluid at 1,200 rpm for 10 minutes, the pellet and about 2 ml of amniotic fluid was added to 5 ml of culture media (Chang's media) in a tissue flask, and cultured in a 37C, 5% CO_2 culture system for 4−5 days until cell growth was observed. The media was changed to a fresh one every 3 days under the guidance of an inverted microscope for 2−3 weeks. When enough cell colonies were obtained, subculture was done: in the presence of mitosis, 10 ng/ml Colcemid 0.5 ml was added and put in the 5% CO_2 culture system for 2−5 hours. The cells were separated from the surface of the flask using Trypsin-EDTA solution. Hypotonic treatment was performed to swell the cells, using 0.075 M KCl. Fixation procedure was repeated three times. Slides were prepared with a small amount of pellet and fixation solution. After air-drying the slides and G-banding, 20−50 cells were selected. Photos were taken at the metaphase and chromosomal analysis was performed. Advanced maternal age, previous birth to chromosomal or congenital anomalies, family history of chromosomal or congenital anomalies, history of neonatal birth or intrauterine fetal death without a known etiology, abnormal maternal serum markers, abnormal ultrasonographic findings indicating chromosomal anomalies, and habitual abortion without a known etiology were indications of amniocentesis. For statistical analysis, χ^2-test was used. $p<0.05$ was considered to be significant.

RESULTS

Age distribution

Fifty-four patients were of maternal age 19 years and under (0.5%), 495 patients were from 20 to 24 (4.5%), 2,811 patients were 25 to 29 (25.5%), 2,989 patients were 30 to 34 (27.2%), 3,735 patients were

Table 1. Age Distribution

Maternal age	No. of patients	%
−19	54	0.49
20−24	495	4.50
25−29	2811	25.54
30−34	2989	27.19
35−39	3735	33.96
40−	916	8.32
Total	11,000	100.00

Table 2. Indications for Prenatal Genetic Amniocentesis

Indications	No. of cases	%
Advanced maternal age (≥35)	4651	42.29
Previous chromosomal abnormality	685	6.23
Previous congenital anomaly	762	6.93
FHx of chromosomal abnormality	109	0.99
FHx of congenital anomaly	157	1.43
Carrier of X-linked recessive disorder	11	0.10
Previous neonatal death or stillbirth	71	0.65
Positive maternal serum marker	3720	33.81
Abnormal US findings*	322	2.93
Drug abuse or X-ray irradiation	74	0.67
Others	438	3.97
Total	11,000	100.00

* Abnormal ultrasonic findings include choroid plexus cyst, omphalocele, duodenal atresia, nuchal fold thickening, nuchal translucency, congenital heart disease, etc.

35-39 (34.0%), and 916 patients were older than 40 (8.3%) (Table 1).

Indications

The most common indications for amniocentesis included advanced maternal age (42.3%), abnormal maternal serum markers (33.8%), previous history of congenital anomaly (6.9%), previous history of chromosomal anomaly (6.2%), and abnormal ultrasonographic findings suggesting chromosomal anomalies (2.9%) (Table 2).

Incidence and changes in indications

The incidence of amniocentesis is steadily increasing. Seventy-six cases were performed in 1988, 81 cases in 1989, 112 cases in 1990, 130 cases in 1991, 210 cases in 1992, 487 cases in 1993, 779 cases in 1994, 1,198 cases in 1995, 3,032 cases in 1996, and 3,032 cases in 1997. In the 1980s, 76.7% of amniocentesis procedures were done due to advanced maternal age, but since 1994, abnormal maternal serum markers have been the most common indication for amniocentesis (Fig. 1 and 2).

Gestational age

In declining order of incidence, amniocentesis was done at 17 gestational weeks in 30.2% of cases, 18 gestational weeks (20.8%), 19 gestational weeks (15.9%), 16 gestational weeks (10.3%), 20 gestational weeks (8.0%), 21 gestational weeks (4.8%), more than 24 gestational weeks (3.7%), 22 gestational weeks (3.1%), 23 gestational weeks (2.1%), and less than 15 gestational weeks (1.2%). The reason for the high incidence in taking amniocentesis after 21 gestational weeks (13.6%) was because of the increasing detection rate of abnormal ultrasonographic findings or maternal serum markers (Fig. 3).

Chromosomal analysis

Abnormal chromosomal findings were observed in 270 cases (2.5%). Numerical aberrations were 164

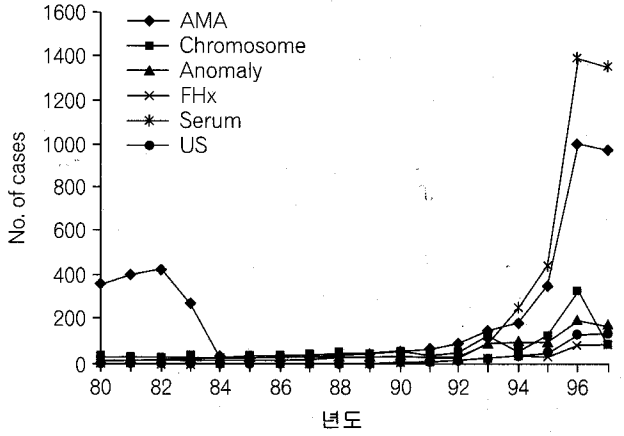

Fig. 2. Annual distribution of amniocentesis cases by indication. AMA, *advanced maternal age; Chromosome, previous chromosomal abnormality history; Anomaly, previous congenital anomaly history; FHx, family history of chromosomal and congenital anomaly; Serum, maternal serum triple marker screening; US, abnormal ultrasonographic findings.*

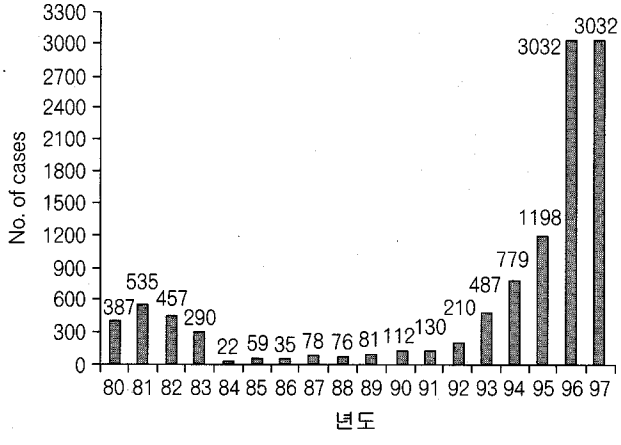

Fig. 1. Annual distribution of amniocentesis cases.

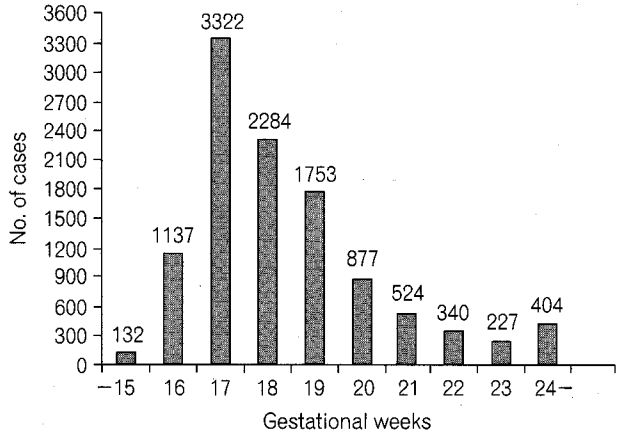

Fig. 3. Distribution of gestational age at amniocentesis.

Table 3. Frequency of Chromosomal Aberration

Karyotype	No.	Percent (%)
Numerical aberration	164	60.74
Autosomal	141	52.22
Trisomy 21	96	35.55
18	33	12.22
13	6	2.22
9	1	0.37
10	1	0.37
Marker	4	1.48
Sex chromosome	22	8.15
45X	10	3.70
47XXX	2	0.75
47XXY	10	3.70
Triploidy 69XXX	1	0.37
Structural aberration	91	33.71
Translocation	83	30.74
Balanced	66	24.44
Robertsonian		
t (13q;14q)	13	4.81
t (13q;21q)	3	1.11
t (14q;21q)	1	0.37
Reciprocal	49	18.14
Unbalanced	17	6.29
Isochromosome	2	0.75
Deletion	6	2.22
Mosaicism	15	5.55
Total	270	100.00

cases, structural aberrations were 91 cases, and mosaicisms were 15 cases. In cases of autosomal numerical disorders, 96 trisomy 21, 33 trisomy 18, and 6 trisomy 13 were observed. In cases of sex chromosomal numerical disorders, 10 45X, 10 47XXY, and 2 47XXX were observed. In cases of translocations, 17 unbalanced translocations, 17 Robertsonian balanced translocations, and 49 reciprocal translocations were observed. Among the 15 mosaicisms, 4 cases were Turner syndrome and 2 cases were Down syndrome (Table 3).

Age distribution of chromosomal analysis

Chromosomal anomalies were found in 2.0% of mothers from age 20-24, 2.1% from 25-29, 2.4% from 30-34, 2.7% from 35-39, and 2.8% over 40 years old. For statistical analysis, 2-test was used. No statistical difference could be found in the maternal age distribution among detected chromosomal anomalies (p value=0.556) (Table 4).

Table 4. Distribution of Chromosomal Aberrations by Maternal Age

Maternal age	Chromosomal aberration	
	No.	%
20-24	11/549	2.00
25-29	60/2811	2.13
30-34	73/2989	2.44
35-39	100/3735	2.68
40-	26/916	2.83
Total	270/11,000	2.45

No statistical difference could be found in the maternal age distribution among detected chromosomal anomalies (p value =0.556).

Table 5. Abnormal Karyotype According to Indication

Indication	Chromosomal aberrations		
	Total	No.	%
Advanced maternal age	4651	124	2.66
Previous chromosomal anomaly	685	14	2.04
Previous congenital anomaly	762	14	1.84
Positive maternal serum marker	3720	83	2.23
Previous neonatal death or stillbirth	71	2	2.81
Abnormal US findings	322	21	6.52
Others	438	12	2.74
Total		270	2.45

Chromosomal anomalies and amniocentesis indications

Chromosomal anomalies were found in 2.7% of 4,651 advanced maternal age patients, in 2.0% of patients with previous history of chromosomal anomaly, in 1.8% of patients with previous history of congenital anomalies, in 2.2% of patients with abnormal maternal serum markers, and in 6.5% of patients who took amniocentesis due to abnormal ultrasonographic findings (Table 5).

DISCUSSION

Since prenatal diagnosis by chromosomal analysis became available using amniocentesis in 1967,[4] it has been increasingly used in the diagnosis and treatment of obstetrical practice between 15 and 18 gestational weeks. According to Golbus, the success rate of fetal cell culture approaches 99.7%,[5] and due to the development of ultrasonography the rate of hemorrhagic amniocentesis has decreased from 15% to 5.2%.[6] In the 1970s and 1980s, the most common indication for amniocentesis was advanced maternal age (35 years old). In the study of Golbus it was 2024/3000 (80%), 1279/2013 (63.9%) in the report of Dacus, while in the study of Bell the rate increased from 38.4% in the 1970s to 57.8% in the 1980s.[5,7,8] In Korea, Ju reported the rate to be 81.7% from 1980 to 1983.[9] In this study, similar findings were observed: 74.5% (1589/2132) of amniocentesis was done due to advanced maternal age from 1980 to 1990.

The incidence of chromosomal abnormalities increased as maternal age advanced. In maternal age over 35 years, the incidence was 1/350 and it increased to 1/100 in maternal age over 40 years.[10] However, if only the age group over 35 is included in amniocentesis, only 20% of Down's syndrome can be detected. Therefore the need for screening in mothers under age 35 who have a high probability of a chromosomally abnormal fetus has been advocated.[11] The incidence of chromosomal abnormalities did not show a significant difference depending on maternal age in this study. The incidence of chromosomal abnormalities in the advanced maternal age group was 2.71%, 2.43% in age 30−34, 2.13% in age 25−29, and 2.00% in age 20−24. Comparatively, more mothers under 34 years of age took amniocentesis due to the progress in ultrasonographic examination and maternal serum markers as screening tests.

There have been reports from NYCR (New York Chromosome Registry) where the changes in practice of amniocentesis from 1984 to 1993 were analyzed.[12] During those 10 years, no significant changes could be observed in the number of advanced maternal age cases taking amniocentesis, but in the group of maternal age younger than 35 years, the rate rose from 1.4% in 1984 to 4.7% in 1993.[12] Some of the reasons for this rise include: a better informed situation of the importance of prenatal genetic diagnosis; an increased number of labs where chromosomal analysis can be done; and progress in prenatal screening tests including ultrasonography and maternal serum markers. In particular, the importance of maternal serum markers in detecting Down syndrome was mentioned.

The MSAFP (maternal serum alpha fetoprotein) test done in the midtrimester shows an abnormally increased value in 3−4% of mothers who take it according to Wenstrom and about 80−85% of these cases result in neural tube defect.[13] In cases of elevated MSAFP levels, there has also been an increase in the number of cases proceeding to amniocentesis, and Crandall reported 21% of elevated MSAFP patients had chromosomal anomaly.[14] Merkatz reported an average 25% decrease in MSAFP levels in Down syndrome,[15] and since then many reports have confirmed the decrease in MSAFP level in trisomies.[16-18] Canick reported a 0.79 times decrease in maternal serum uE2 level in Down syndrome.[19] Several reports have confirmed the positive relationship between hCG and chromosomal abnormalities, and currently an elevated level of hCG is used in the detection of aneuploidies in clinical practice.[20] Yang reported that the most common indication of amniocentesis from 1993 has changed from advanced maternal age to abnormal maternal serum markers.[21] According to the reports of Ogueh, 42.1% of amniocentesis done between 1991−1994 was due to advanced maternal age and 56.1% was due to abnormal maternal serum markers. In this study, ever since the early 1990s when maternal serum markers were used, 44.8% of amniocentesis was done due to abnormal maternal serum markers.

In cases of previous birth to congenital or chromosomal anomalies, or a history of congenital or chromosomal anomalies, there should be a proper diagnosis in consideration of psychiatric stress that could affect the family. In this study, 6.2% of amniocentesis was done due to previous birth to chromosomal anomalies, and 6.9% of amniocentesis was done due to previous birth to congenital anomalies.

Progress in ultrasonographic examination has also resulted in an increased number of candidates taking amniocentesis.[22] In this study, 2.93% of amniocentesis was done due to abnormal findings depicted in ultrasonographic examination. It is still a matter

of debate whether or not to include ultrasonographic findings suggesting fetal choroid plexus cyst in the category of independent variables of trisomy 18.[23-26] In the study of Yang, 7.9% of patients taking amniocentesis due to abnormal findings in ultrasonographic examination independent of maternal age or maternal serum markers had chromosomal anomalies. In this study, 6.5% of patients who took amniocentesis due to abnormal ultrasonographic findings had chromosomal anomalies. These results strongly advocate the need for amniocentesis in cases of abnormal ultrasonographic findings.

According to Yagel, 92.2% of Down syndrome can be screened in consideration of maternal age, maternal serum triple test results, and midtrimester targeted-organ screening by ultrasonography.[27] Holoprosencephaly, ventriculomegaly, agenesis of the corpus callosum, thickened nuchal skin fold or nuchal edema, cystic hygroma, congenital heart disease, esophageal atresia, duodenal atresia, diaphragmatic hernia, omphalocele, and nonimmune hydrops are important ultrasonographic findings requiring amniocentesis.[28]

Of all the amniocentesis procedures done, 4.3% were found to be chromosomal anomalies in the report of NICHD.[29] This value varies according to different studies, from 1.0% to 6.3%.[29-31] In this study, 2.46% of all cases were found to have chromosomal anomalies, which was similar to the data of Yang and Bell. Dacus reported 1.0% (20/2000) chromosomal anomalies, of which 11 were Down syndrome.[7] Cruickshank reported 2.0% to have Down syndrome and 3.0% to have chromosomal anomalies in maternal age older than 35 years, where this rate rose to 4.8% and 7.2% respectively in maternal age over 40 years.[32] In this study, 2.71% showed chromosomal anomalies in the advanced maternal age group, and this value was 2.4% in maternal age younger than 35 years. Trisomy 21 was the most common anomaly found (35.6%), followed by trisomy 18 (12.2%) and trisomy 13 (2.2%). In cases of sex chromosomal anomalies, 10 cases of 45X (3.7%) and 10 cases of 47XXY (3.7%) were found. Chromosomal structural anomalies were found in 8.3/1000, a value higher than the 2.24/1,000 reported by Hook.

From the aspect of cost-efficacy in Down syndrome detection using amniocentesis, Glass reported screening of women older than 40 years to be most efficient, whereas Hegard and Carter suggested older than 35 years, and Andreano and McCollum suggested 32 years.[33-36] Holmes suggested amniocentesis in all women over 35 years old, and that by the end of this century the age should be corrected to 30 years.[37]

In summary, genetic amniocentesis as a prenatal diagnostic test in Korean women has risen 10-fold in the last 10 years (1988−1998). The primary indication of amniocentesis in the past was advanced maternal age. However, due to the development of maternal serum markers and early fetal abnormalities found through more sensitive ultrasonic technology, the indications for amniocentesis are changing. If we look at recent statistics, the most common indication for amniocentesis is now as a result of abnormal maternal serum markers. There has also been an increase in abnormal early findings that are detected by ultrasound and that subsequently necessitate amniocentesis. Therefore, screening for possible amniocentesis now comprises more women aged 34 and under than previously, when the advanced maternal age group (35 and over) was most prevalent.

REFERENCES

1. Schatz F. Eine besondere art von ein seitiger polyhydamnic mit anderseitiger oligohydramnie bei zwillingen. Arch Gynaekol 1982;19:329-37.
2. Fuchs F, Riis P. Antenatal sex determination. Nature 1956; 177:330-4.
3. Steele MW, Breg WR. Chromosome analysis of human fluid cells. Lancet 1966;1:383-5.
4. Jacobsen CB, Barter RH. Intrauterine diagnosis and mangement of genetic defects. Am J Obstet Gynecol 1967; 99:796-807.
5. Golbus MS, Loughman WD, Epstein CJ, Halkasch G, Stephens JD, Hall BD. Prenatal genetic diagnosis in 3000 amniocentesis. N Engl J Med 1979;300:157-63.
6. Harrison R, Campbell S. Risks of feto-maternal hemorrhage resulting from amniocentesis with and without ultrasound placental localization. Obstet Gynecol 1975;86:89-91.
7. Dacus JV, Wilroy RS, Summitt RL, Garbaciak JA, Abdella TN, Spiannato JA, et al. Genetic amniocentesis: A twelve year's experience. Am J Med Genet 1985;20:443-52
8. Bell JA, Pearn JH, Wilson BH, Ansford AJ. Prenatal cytogenetic diagnosis-a current audit 1987 A review of 2000 cases of prenatal cytogenetic diagnosis after amniocentesis and comparisons with early experience. Med J Aust 1987; 146:12-5.
9. Ju KS, Kim SB. Chromosome analysis of the mid-preg-

nancy amniocentesis. Korean J Obstet Gynecol 1993;36: 3576-88.
10. Little BB, Ramin SM, Cambridge BS, Schneider NR, Cohen DS, Snell LM, et al. Risk of chromosomal abnormalities with emphasis in liveborn in offspring of very young mothers. Am J Hum Genet 1995;57:1178-83.
11. Adams MM, Erickson JD, Layde PM, Oacley P. Down's syndrome: Recent trends in the United States. JAMA 1981;246:758-60.
12. Olsen CL, Cross PK. Trends in the use of prenatal diagnosis in New York state and the impact of biochemical screening on the detection of Down syndrome: 1984-1993. Prenat Diagn 1997;17:1113-24.
13. Wenstrom KD, Williamson RA, Grant SS, Hudson JD, Getchell JP. Evaluation of multiple-marker screening for Down syndrome in a statewide population. Am J Obstet Gynecol 1993;169:793-7.
14. Crandall BF, Robinson RD, Lebherx TB, King W, Schroth PC. Maternal serum alpha-fetoprotein screening for the detection of neural tube defects. West J Med 1983;138: 524-30.
15. Merkatz IR, Nitowsky HM, Macri JN, Johnson WE. An association between low maternal serum alphafetoprotein and fetal chromosome abnormalities. Am J Obstet Gynecol 1984;148:886-94.
16. Dimaio MS, Baumgarten A, Greenstein R, Saal H, Mahoney M. Screening for fetal Down syndrome in pregnancy by measuring maternal serum alpha-fetoprotein levels. N Engl J Med 1987;317:342-6.
17. Palomaki GE, Haddow JW. Maternal serum alphafetoprotein, age, and Down syndrome risk. Am J Obstet Gynecol 1987;156:460-3.
18. Wald NJ, Cuckle HS. sFP and age screening for Down syndrome. Proceedings of the American Society of Human Genetics Conference. October 1987. Am J Hum Genet 1988;31:197-209.
19. Canick JA, Knight GJ, Palomaki GE, Haddow JE, Cuckle HS, Wald NJ. Low second trimester maternal serum unconjugated oestriol in pregnancies with Down syndrome. Br J Obstet Gynecol 1987;95:330-3.
20. Bogart HM, Pandian MR, Jones CW. Abnormal maternal serum chorionic gonadotropin levels in pregnancies with fetal chromosome abnormalities. Prenat Diagn 1987;7: 623-30.
21. Yang YH, Kwon HK, Kim SK, Park YW, Cho JS, Kim IK, et al. Prenatal genetic diagnosis in 2,000 amniocentesis. Korean J Obstet Gynecol 1999;42:65-71.
22. Vintzileos AM, Campbell WA, Nichimson DJ, Weinbaum PJ. Antenatal evaluation and management of ultrasonographically detected fetal anomalies. Obstet Gynecol 1987; 69:640-60.
23. Nicolaides KH, Rodeck CH, Gosden CN. Rapid karyotyping in nonlethal malformations. Lancet 1986;i:283-7.
24. Porto M, Murata Y, Warneke LA, Keegam KA. Fetal choroid plexus cysts: An Independent risk factor for chromosomal Anomalies J Clin Ultrasound 1993;21:103-8.
25. Deroo TR, Harris RD, Sargent SK, Denhom TA, Crow HC. Fetal choroid plexus cysts:prevalance, clinical significance and sonographic appearance. Am J Roentgenol 1988;151:1179-81.
26. Nadel AS, Bromley BS, Frigolette FD, Estroff JA, Benacerrraf BR. Isolated choroid plexus cysts in the second-trimester fetus:Is amniocentesis really indicated? Radiology 1992;185:545-8.
27. Yagel S, Anteby EY, Celnikier DH, Ariel I, Chaap T, Neriah ZB. The role of midtrimester targeted fetal organ screening combined with the "triple test" and maternal age in the diagnosis of trisomy 21; a retrospective study. Am J Obstet Gynecol 1998;178:40-4.
28. Hogge WA, Thiagrajah S, Ferguson II JE, Schnatterly PT, Herbert GM. The role of ultrasonography and amniocentesis in the evaluation of pregnancies at risk for neural tube defects. Am J Obstet Gynecol 1989;161:520-4.
29. NICHD National Registry for Amniocentesis Study Group. Midtrimester amniocentesis for prenatal diagnosis. safety and accuracy. JAMA 1976;236:178-90.
30. Simpson NE, Dallaire L, Meller JR. Prenatal diagnosis of genetic disease in Canada: Report of a collaborative study. Can Med Assoc J 1976;15:739-46.
31. Crandall BF, Lebherz TB. Prenatal genetic diagnosis in 350 amniocentesis. Am J Obstet Gynecol 1976;48:158-62.
32. Cruikshank DP, Varner MW, Cruikshank JE, Grant SS, Donnelly E. Midtrimester amniocentesis. Am J Obstet Gynecol 1983;146:204-11.
33. Glass N. Economic aspects of the prevention of Down's syndrome. In: Bailey NTJ, Thompson M, editors. System aspects of health planning. Amsterdam (North-Holland): North-Holland Press; 1975. p.107.
34. Hagard S, Carter FA. Preventing The Birth of infants with Down's syndrome: A cost-benefit analysis. Br Med J 1976; 1:753-6.
35. Mikkelsen M, Nielsen G, Rasmussen E. Cost-effectiveness of antenatal screening for chromosome abnormalities. In: Scrimgeour JB, editor. Towards the prevention of fetal malformation. Edinburgh: Edinburgh University Press; 1978. p.74.
36. Andreano RL, McCollum DW. A benefit-cost analysis of amniocentesis. Soc Biol 1983;30:347-73.
37. Holmes LB. Genetic counselling for the older pregnancy woman: new data and questions. N Engl J Med 1978; 298:1419-21.