ความชุกของภาวะแอนนูพลอยด์ที่พบบ่อยและความผิดปกติของโครโมโซมเพศของทารกในครรภ์จากการเจาะตรวจน้ำคร่ำ

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บทคัดย่อ

ความผิดปกติของจำนวนโครโมโซมเป็นความผิดปกติที่พบบ่อยที่สุดในห้องปฏิบัติการมนุษย์พันธุศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี การศึกษานี้มีวัตถุประสงค์เพื่อประเมินความชุกของความผิดปกติของจำนวนโครโมโซม ชนิดไทรโซมี 13, 18 และ 21 และความผิดปกติของโครโมโซมเพศของทารกในครรภ์ของหญิงตั้งครรภ์ ซึ่งแบ่งเป็น 2 กลุ่ม ได้แก่ กลุ่มหญิงตั้งครรภ์ที่มีอายุตั้งแต่ 35 ปีขึ้นไป และกลุ่มหญิงตั้งครรภ์ที่มีอายุน้อยกว่า 35 ปี การวิจัยนี้เป็นการวิเคราะห์ตัวอย่างน้ำคร่ำของหญิงตั้งครรภ์ที่ส่งตรวจวิเคราะห์โครโมโซมในโรงพยาบาลรามาธิบดี ระหว่างเดือนมกราคม พ.ศ. 2555 ถึงเดือนธันวาคม พ.ศ. 2564 จำนวน 6,804 ตัวอย่าง เพื่อตรวจหาความผิดปกติของจำนวนโครโมโซมคู่ที่ 13, 18, 21, X และ Y ซึ่งทำโดยการย้อมด้วยเทคนิค GTG banding ผลการวิจัยพบว่าหญิงตั้งครรภ์ 280 ราย (ร้อยละ 4.12) มีความผิดปกติของจำนวนโครโมโซมที่พบบ่อยและความผิดปกติของจำนวนโครโมโซมเพศ โดยพบความผิดปกติของจำนวนโครโมโซม เท่ากับ ร้อยละ 2.96 และมีความผิดปกติชนิดไทรโซมี 21 บ่อยที่สุด คือ 92 ราย (ร้อยละ 1.35) ความผิดปกติของจำนวนโครโมโซมอื่น ได้แก่ ไทรโซมี 18 (50 ราย, ร้อยละ 0.73), ไทรโซมี 13 (16 ราย, ร้อยละ 0.24), กลุ่มอาการเทิร์นเนอร์ (13 ราย, ร้อยละ 0.19), กลุ่มอาการไคลน์เฟลเทอร์ (18 ราย, ร้อยละ 0.26), กลุ่มอาการไทรโซมีเอกซ์วายวาย (4 ราย, ร้อยละ 0.06) และกลุ่มอาการทริปเพิลเอกซ์ (8 ราย, ร้อยละ 0.12) พบความผิดปกติของโครงสร้างโครโมโซมในผู้ป่วย 79 ราย (ร้อยละ 1.16) และหญิงตั้งครรภ์ช่วงอายุ 35-39 ปี มีอุบัติการณ์ของความผิดปกติของโครโมโซมสูงที่สุด ผลการวิจัยนี้แสดงว่าหญิงตั้งครรภ์ช่วงอายุ 35-39 ปี มีความ

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เสี่ยงของความผิดปกติของโครโมโซมเพิ่มขึ้นอย่างมีนัยสำคัญ โดยเฉพาะความผิดปกติชนิดไทรโซมี 21 และความผิดปกติของโครงสร้างโครโมโซมพบในกลุ่มหญิงตั้งครรภ์ที่มีอายุตั้งแต่ 35 ปีขึ้นไป

คำสำคัญ: ความผิดปกติของโครโมโซมของทารกในครรภ์ อายุของมารดาที่ตั้งครรภ์ การตรวจวินิจฉัยความผิดปกติของโครโมโซมทารกในครรภ์ ไทรโซมี 21

Prevalence of Common Aneuploidies and Sex Chromosome Abnormalities in Second Trimester Amniocentesis

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Abstract

Aneuploidy represents the predominant chromosomal abnormalities observed at the Human Genetic Laboratory, Faculty of Medicine Ramathibodi Hospital. This study aimed to evaluate the prevalence of common aneuploidies, including trisomies 13, 18, 21 and sex chromosome abnormalities amongst two maternal age groups: ≥ 35 years and < 35 years old. We analyzed 6,804 prenatal amniotic fluid specimens, collected from Ramathibodi Hospital during January 2012 and December 2021, for aneuploidies of chromosomes 13, 18, 21, X, and Y by using the GTG banding technique. Our results identified 280 cases (4.12%) with common aneuploidies and sex chromosome abnormalities. Among the numeric chromosomal abnormalities cases (2.96%), trisomy 21 was the most prevalent, reportedly found in 92 patients (1.35%). The proportion of other abnormalities were listed as: trisomy 18 (50 cases, 0.73%), trisomy 13 (16 cases, 0.24%), Turner syndrome (13 cases, 0.19%), Klinefelter syndrome (18 cases, 0.26%), XYY syndrome (4 cases, 0.06%), and triple X syndrome (8 cases, 0.12%). We also identified structural chromosomal abnormalities in 79 cases (1.16%). In conclusion, women with age ranges between 35-39 years possessed the highest incidence of chromosomal abnormalities. These findings indicated a significant surge in the risk of chromosomal anomalies within the maternal age between 35-39 years. Trisomy 21 and structural chromosome abnormalities were predominant in the advanced maternal age group (≥ 35 years old).

Keywords: Fetal chromosome aberrations, Maternal age, Prenatal diagnosis, Trisomy 21

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Introduction

The unique structure of chromosomes allows cytogeneticists to identify the characteristics of genetic materials at the cellular level. Chromosomes allow DNA to be accurately copied during cell division. A range of chromosome anomaly can be physical and intellectual abnormalities.[1] In Thailand, fetal chromosomal abnormalities have been studied by using amniotic fluid samples of pregnant women during the second trimester, and the chromosomal abnormality incidence of 2.5-3.3% was reported. These abnormalities include trisomies 13, 18, 21, sex chromosome aneuploidies, and structural rearrangements[2-5] Chromosomal abnormalities can be categorized as structural and numerical abnormalities.[6] The factors leading to chromosomal abnormalities vary and can arise if either the father or the mother is a carrier. It may be caused by abnormal cell division during meiosis (nondisjunction), which is the most common diagnosis in advanced maternal age. Thus, chromosomal abnormalities are of significant concern. All pregnant women, especially those at high risks, should be recommended for chromosome screening to determine the risk of fetal chromosomal abnormalities.[5] The patients are recommended to follow a prenatal diagnosis, determining the number and structure of the chromosomes. Genetic information and chromosomal abnormalities allow physicians to give appropriate advice and care for the patients and their families. Depending on the gestational age, various fetal specimens, including chorionic villus, fetal blood, and amniotic fluid, are used for karyotyping. Amniocentesis is commonly requested by physicians to achieve genetic information for prenatal diagnosis. It is relatively safe and less complication rate, and is usually performed between 14 to 20 weeks of gestation. The conduction of amniocentesis between 11-13 weeks of gestation may possess risks including a miscarriage rate of 0.1% to 0.3%.[7-8] In the past, prenatal chromosome analysis was approached by using quantitative fluorescent polymerase chain reaction (QF-PCR), which demonstrated the dramatically high concordant result of QF-PCR and cytogenetic assay.[9] Currently, advancement of prenatal diagnostic tools for genetic testing have been deployed including QF-PCR, chromosomal microarray (CMA), and next generation sequencing based technology.[10-13]

This study examined the common aneuploidies and sex chromosome abnormalities in second trimester amniocentesis samples. The correlation between fetal chromosomal abnormalities and maternal age was also analyzed to get potential association of genetic information and maternal age.

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Materials and methods

A total of 6,804 pregnant women who underwent amniocentesis during January 2012 to December 2021 were registered for sampling. Amniotic fluid (AF) samples were sent to the Human Genetics Laboratory, Faculty of Medicine Ramathibodi Hospital, for analysis of aneuploidy in chromosomes 13, 18, 21, X, and Y. Karyotyping was performed by using GTG banding technique. The analysis followed conventional cytogenetic principles based on the International System for Human Cytogenetic Nomenclature (ISCN 2020) standard. Maternal age groups were divided into two subgroups. The first group comprised pregnant women below 35 years old, while the second group, termed "advanced maternal age," included those with 35 years of age and older.

Fetal chromosomal abnormalities were classified according to numeric chromosomal abnormalities and further classified into autosomal and sex chromosomal anomalies. Variations considered normal, such as the pericentric inversion of chromosomes 9 and Y, were excluded from the category of abnormalities.[14]

To analyze maternal age-specific rates of fetal chromosomal abnormalities in advanced maternal age (AMA) pregnancies, maternal ages beyond 35 were segmented in five-year intervals. Only pregnancies in the AMA category were considered for amniocentesis to determine the incidence rate of fetal chromosomal abnormalities. The study results were statistically analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered as statistically significance.

Results

Of the 6,804 pregnant women who underwent amniocentesis, the ages range were from 15 to 51 years and the median age was 36 years. The age distribution of all study participants was shown in Table 1 and 2. According to the fetal chromosomal analysis, 6,524 cases (95.88%) were normal, while 280 cases (4.12%) displayed abnormal fetus chromosomes. Of the patients with abnormal results, 2.96% had numeric chromosomal abnormalities. These percentages indicated a statistical correlation between maternal age and specific numerical chromosomal abnormalities, with trisomies 21, 18, and structural chromosome abnormalities being the most common. The standard errors from logistic regression equations showed that trisomy 21 and structural chromosomal abnormalities diagnosed at amniocentesis did not have any significant correlation with maternal age.

The incidence rates of chromosomal abnormalities are detailed in Table 3. The incidence rates of numeric autosomal and sex chromosomal anomalies were segmented in five-year intervals, ranging from ages 15 to 51. Trisomy 21 showed an incidence rate

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of 10 and 68 out of 1,000 cases for 35-39 and ≥ 45 years old, respectively. Trisomy 18 showed an incidence rate of 3 and 68 out of 1,000 patients for 35-39 and ≥ 45 years old, respectively. Trisomy 13 showed an incidence rate of 1 and 23 out of 1,000 patients for 35-39 and ≥ 45 years old, respectively, which is a sharp increase. Four study subjects possessed sex chromosomal anomalies. Due to the small number of subjects with these anomalies, correlation analysis between fetal chromosomal abnormalities and age was not feasible. The logistic regression analysis revealed a close correlation between age groups and the incidence of trisomies 21, 18, and 13.

The pregnant participants were categorized into seven age groups including of (i) < 20, (ii) 20-24, (iii) 25-29, (iv) 30-34, (v) 35-39, (vi) 40-44, and (vii) > 44 years old. The percentage of chromosomal abnormalities during five-year intervals of maternal age, ranging from 15 to 51 years old, was demonstrated in Fig. 1 In the 35-39 years old maternal age group, numerical abnormalities were detected in both autosomes and sex chromosomes. In numerical abnormalities of autosomes, 0.65%, 0.28%, and 0.09% were detected in trisomies 21, 18, and 13, respectively. However, sex chromosome abnormalities were found in 0.32% of this group. Structural chromosomal abnormalities were demonstrated in 0.72% of cases. Thai pregnant women in the age range of 35-39 years had the highest percentage of both numerical and structural chromosomal abnormalities.

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Table 1 The percentage of chromosomal abnormalities in amniocentesis amongst five year-intervals ranged from 15 to 51 years.

Maternal age (Years old)	Number of patients (%)	Number of aneuploidies detected by cytogenetics analysis								
		Trisomy 21	Trisomy 18	Trisomy 13	X Monosomy	XYY Triploidy	XXY Triploidy	XXX Triploidy	Structural chromosome abnormalities	Total
< 20	8 (0.12%)	0	1 (0.01%)	0	0	0	0	0	0	1 (0.01%)
20-24	50 (0.73%)	0	0	0	0	0	0	0	2 (0.03%)	2 (0.03%)
25-29	251 (3.69%)	3 (0.04%)	4 (0.06%)	4 (0.06%)	6 (0.09%)	0	1 (0.01%)	1 (0.01%)	4 (0.06%)	23 (0.34%)
30-34	1182 (17.37%)	13 (0.19%)	12 (0.18%)	4 (0.06%)	2 (0.03%)	2 (0.03%)	5 (0.07%)	0	18 (0.26%)	56 (0.82%)
35-39	4334 (63.70%)	44 (0.65%)	19 (0.28%)	6 (0.09%)	5 (0.07%)	1 (0.01%)	11 (0.16%)	5 (0.07%)	49 (0.72%)	140 (2.06%)
40-44	935 (13.74%)	29 (0.43%)	11 (0.16%)	1 (0.01%)	0	1 (0.01%)	1 (0.01%)	2 (0.03%)	6 (0.09%)	51 (0.75%)
≥ 45	44 (0.65%)	3 (0.04%)	3 (0.04%)	1 (0.01%)	0	0	0	0	0	7 (0.10%)
Total	6804 (100.00%)	92 (1.35%)	50 (0.73%)	16 (0.24%)	13 (0.19%)	4 (0.06%)	18 (0.26%)	8 (0.12%)	79 (1.16%)	280 (4.12%)

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Table 2 The percentage of chromosomal abnormalities in amniocentesis between two subgroups of ages.

Maternal age (Years old)	Number of patients (%)	Number of aneuploidies detected by cytogenetic analysis								
		Trisomy 21	Trisomy 18	Trisomy 13	X Monosomy	XYY Triploidy	XXY Triploidy	XXX Triploidy	Structural chromosome abnormalities	Total
< 35	1491 (21.91%)	16 (0.24%)	17 (0.25%)	8 (0.12%)	8 (0.12%)	2 (0.03%)	6 (0.09%)	1 (0.01%)	20 (0.29%)	81 (1.19%)
≥ 35	5313 (78.09%)	76 (1.12%)	33 (0.49%)	8 (0.12%)	5 (0.07%)	2 (0.03%)	12 (0.18%)	7 (0.10%)	54 (0.79%)	199 (2.92%)
Total	6804 (100.00%)	92 (1.35%)	50 (0.73%)	16 (0.24%)	13 (0.19%)	4 (0.06%)	18 (0.26%)	8 (0.12%)	74 (1.09%)	280 (4.12%)

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Table 3 Chance of aneuploidies detected by cytogenetic analysis (incidences per 1,000).

Maternal age (Years old)	Number of patients	Chance of aneuploidies detected by cytogenetic analysis (incidences per 1,000)							
		Trisomy 21	Trisomy 18	Trisomy 13	X Monosomy	XYY Triploidy	XXY Triploidy	XXX Triploidy	Structural chromosome abnormalities
< 20	8	0	125	0	0	0	0	0	0
20-24	50	0	0	0	0	0	0	0	40
25-29	251	12	16	16	24	0	4	4	16
30-34	1182	11	10	3	2	2	4	0	15
35-39	4334	10	3	1	1	0	3	1	11
40-44	935	31	12	1	0	1	1	2	6
≥ 45	44	68	68	23	0	0	0	0	0
Total	6804								

Table 4 Parameters and standard errors of logistic regression equations.

Parameter	Trisomy 21	Trisomy 18	Trisomy 13	Sex chromosome abnormalities	Structural chromosome abnormalities
p-value	.291	.038*	.007*	.001*	.285

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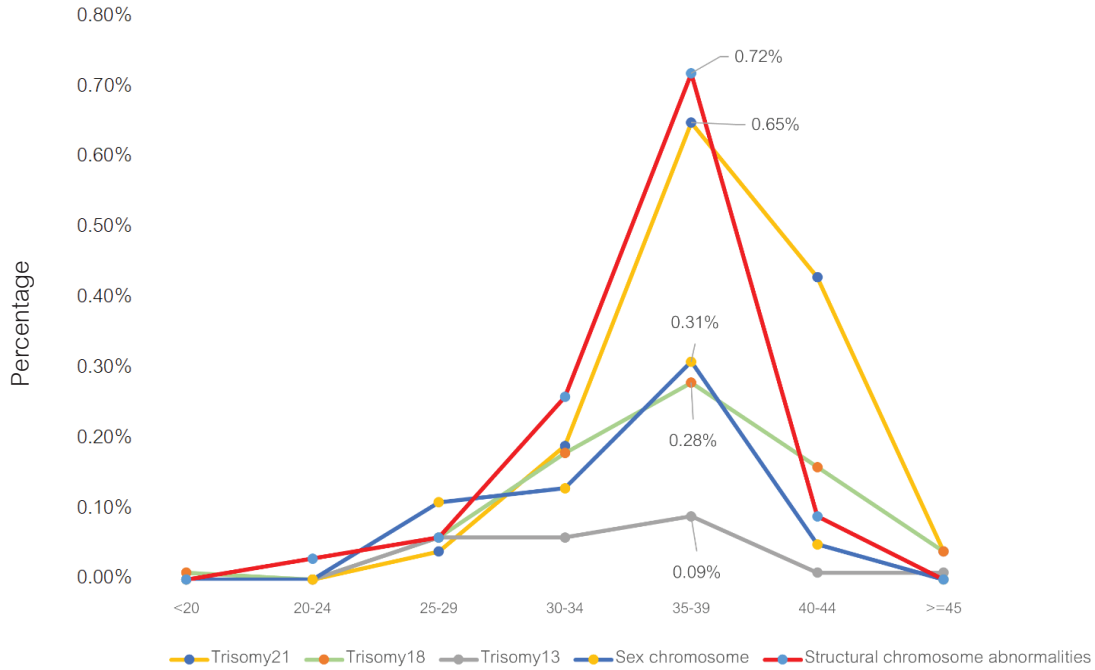


Fig. 1 The percentage of chromosomal abnormalities amongst five year-intervals ranged from 15 to 51 years old.

Discussion

Multiple studies have indicated a close correlation between common aneuploidies and maternal age. In our study, cytogenetic analysis was performed on 6,804 amniotic fluid samples of Thai pregnant women. Our results indicated that 92 (1.35%) were trisomy 21, 50 (0.73%) were trisomy 18, and 16 (0.24%) were trisomy 13. Additionally, among the sex chromosomal aneuploidies, 13 cases (0.19%) were Turner syndrome, 18 (0.26%) were Klinefelter syndrome, 4 (0.06%) were XYY syndrome, and 8 (0.12%) were triple X syndrome. We identified structural chromosome abnormalities in 79 cases (1.16%). This finding was aligned with the reported rates of numerical autosomal and sex chromosomal abnormalities from the 2021 study.[15]

The data from a Canadian prenatal diagnosis laboratory showed that 1.79% of chromosomal abnormalities were detected in advanced maternal age (≥ 35 years) group and in this group, 21% of all abnormalities are structural rearrangements and less than half of all abnormalities are trisomy 21.[16] The report from an *in vitro* fertilization laboratory in the United States concluded that

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common abortus karyotypes in first trimester miscarriage were trisomies 22 (3.8%), 16 (4.5%), and 15 (5.2%) while viable trisomies were observed in chromosomes 13, 18 and 21.[17]

A study reported fetal chromosomal abnormalities in 15,381 Korean pregnant women of advanced maternal age.[18] The study highlighted that the risk of trisomies 21 and 18 significantly increased with advancing maternal age. The data of 479 amniotic fluid samples from a referral laboratory in Mumbai, India during 2015-2016, revealed that chromosomal abnormality was detected in 62 cases (12.94%) while aneuploidy was found in 77.42% and trisomy 21 was the most common abnormalities detected (64.58%).[19] The report from a multicenter study of chromosomal abnormalities in Japan during 2008-2015 demonstrated that trisomy 21 showed the highest termination of pregnancy rate (93.8%) followed by trisomy 18 (84.5%) and trisomy 13 (71.9%).[20] Cytogenetic study of amniotic fluid cells in Iranian women showed that trisomies 21, 18, and 13 were detected for 4.4%, 0.57%, and 0.24%, respectively.[21] In European countries, the total prevalence of live birth for trisomies 21, 18, and 13 were 11.2, 1.04, and 0.48, respectively.[22]

For Thai data, fetal chromosomal abnormalities of amniocentesis in 304 Thai pregnant women were reported.[5] They showed a considerable increase in trisomies 21 and 18, in advanced maternal age. In Thai data derived from chorionic villus samples, trisomy 18 emerged as the most prevalent chromosomal abnormality.[23] This finding is consistent with our observations regarding trisomies 13 and 18, as well as, sex chromosomal anomalies in different maternal age groups. A significant correlation was observed between trisomies 13, 18, and sex chromosomal anomalies in mothers aged 35 and older, as supported by the 2021 report.[24] Notably, an 80% surge in Down syndrome incidence was reported in mothers younger than 35 years of age.[15-26] This is in line with our study, which observed an increased incidence of Down syndrome across all age groups. Thus, no significant correlation was found between maternal age and the incidence of trisomy 21 or structural chromosomal abnormalities across the studied age groups.[27] Nevertheless, pregnant women aged 35 and older remain at risk of bearing a child with chromosomal abnormalities. As a preventive measure against fetal anomalies, it is crucial to screen all pregnant women for potential abnormalities. There remains an inherent risk of conceiving a child with chromosomal abnormalities.

Conclusions

The prenatal chromosome abnormalities analysis conducted at the Human Genetic Laboratory, Faculty of Medicine Ramathibodi Hospital revealed

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a 4.12% incidence rate of chromosomal abnormalities. Of these, 2.96% were numeric abnormalities and 1.16% were structural abnormalities. Trisomies 21 and 18 have emerged as the most prevalent numeric chromosomal abnormalities. The risk of chromosomal anomalies showed a significant increase according to a rise in the maternal age range of 35-39 years. In the advanced maternal age group (≥ 35 years), Down syndrome and structural chromosome abnormalities were most frequently reported.

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