**Comparison of array comparative genomic hybridization and karyotyping in the first trimester screening at the high-risk pregnancies**

Sara Masihi 1, Elahe Shirazi1\*, Farideh Moramezi 1, Najmieh Saadati 1, Mojgan Barati 1

1 Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical

Sciences, Ahvaz, Iran

**Corresponding author:**Dr. Elahe Shirazi

Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical

Sciences, Ahvaz, Iran  
Tel: 09144042058

**Abstract**

**Purpose:** This study aimed to compare CGH array and karyotype for prenatal diagnosis in high-risk individuals in the first trimester screening.

**Materials and Methods:** The present cross-sectional descriptive prospective study was performed on high-risk mothers screened in the first trimester of pregnancy. Individuals were allocated into two groups under karyotype and CGH array. Because this study is based on genetic testing data, it does not require a follow-up. Information on age, number of pregnancies, history of abortion, history of disease and screening results were collected and analyzed. Data analysis was done using SPSS Version 22 (IBM).

**Results:** In total 247 cases were analyzed with 128 cases in the karyotype group and 119 cases in the CGH group. 116 samples (90.6%) in the karyotype group and 99 samples (83.2%) in the CGH group showed a normal karyotype. 4.2% (5 samples) and 7.9% (10 samples) of chromosomal abnormalities were trisomy in the CGH group and the karyotype group, respectively. CGH array analysis on chromosomal abnormalities identified copy number variation (CNV) in about 9.2% (11 samples) of cases. In terms of risk factors structural chromosomal, there was a statistically significant relationship in terms of history of disabled children in the family, maternal age, history of anomalies, screening of the first trimester of pregnancy, and increased NT (p<0.05).

**Conclusions:** High-resolution arrays specifically prevented fetal malformations. Until now, normal prenatal chromosome analysis has been shown a relatively standard method but CGH may be helpful to specialists in diagnosing chromosomal abnormalities, especially in unknown chromosomal abnormalities.

**Keywords:** Prenatal diagnosis, First trimester, High risk, karyotyping

**Introduction**

The development of molecular genetics has significantly reduced the number of births with genetic defects, and mothers should seek diagnostic tests after 11 weeks of gestation for greater reassurance ([1](#_ENREF_1), [2](#_ENREF_2)). About 40,000 amniocentesis and chorionic villus samples are processed each year in the UK, predominantly due to screening for the prenatal detection of chromosomal abnormalities ([3](#_ENREF_3), [4](#_ENREF_4)). Of these, the vast majority have a normal karyotype with complete microscopic analysis. A small number of cases with chromosomal abnormalities have been identified that 80% are autosomal trisomies (involving chromosomes 13, 18, 21) ([5](#_ENREF_5), [6](#_ENREF_6)).

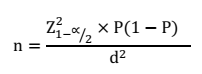
The remaining abnormal karyotypes are changes in the number of sex chromosomes and chromosomal structural rearrangements such as deleted, amplified, inverted, and balanced and unbalanced translocation. Although microscopic analysis is a valid method, it has several limitations ([7](#_ENREF_7)).

Due to the requirement for cell culture, the average reporting time for results in the UK can be up to 14 days. Furthermore, microscopic karyotyping is labour intensive and therefore costly, needs skilled interpretation, and is not easily amenable to automation. This method is based on CNV’s size up to 10Mb ([8](#_ENREF_8), [9](#_ENREF_9)).

Comparative genomic hybridization (CGH) is a molecular cytogenetic technique for analyzing copy number variations (CNVs) relative to ploidy level in the DNA of a test sample compared to a reference sample, deprived of the requirement for culturing cells ([10](#_ENREF_10), [11](#_ENREF_11)). This method allows the identification of similarities and unknowns related to fetal genetic diseases, such as chromosomal abnormalities and aneuploidy in prenatal diagnosis and selection of a complete fetus for this technique ([12](#_ENREF_12)). In a study, CGH array analysis on embryos with multiple abnormalities recognized genomic rearrangements in about 16% of cases that had not been detected by karyotype analysis ([13](#_ENREF_13)). In the present study, we compared CGH array and karyotype for prenatal diagnosis in high-risk individuals in the first-trimester screening.

**Material and methods**

This descriptive cross-sectional study was examined in high-risk mothers during the first trimester of pregnancy. The study protocol was accepted by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences with the code of IR.AJUMS.HGOLESTAN.REC.1399.068. According to a study by schaeffer et al., the sample size was calculated based on the following formula:





Pregnant women who underwent amniocentesis and chorionic villus sampling (CVS) in the first trimester of pregnancy due to high risk in first trimester screening or abnormal ultrasound in the first trimester or abnormalities in the previous baby were included in the study. Women with high-risk pregnancy in the first trimester screening, increased NT in the first trimester ultrasound, or abnormalities in previous pregnancies were included in the study. Based on personal consent for screening test, individuals were divided into two groups under karyotype and CGH array. Both CGH array and karyotype tests were explained to individuals, and in some cases, especially for anomalies, the CGH array was strongly recommended, and decisions were made based on cost and patient consultation. Because this study is based on genetic testing data, it does not require a follow-up. Information on age, number of pregnancies, history of abortion, history of disease and screening results were collected and analyzed.

**Statistical Analysis**

Data analysis was performed using SPSS Version 22 (IBM). To describe the data, the mean and standard deviation or median and mid-quarter amplitude in quantitative variables and frequency and percentage in qualitative variables were used. Normal distribution of the quantitative data was tested with the Kolmogorov–Smirnov test. Due to the abnormality of the data distribution in this study, Kruskal-Wallis and Mann-Whitney nonparametric tests were used to analyze the results. Spearman's correlation coefficient and chi-square tests were used to determine the association between the variables. P value<0.05 was considered to be significant.

**Results**

The mean and standard deviation of age in the karyotype and GCH groups were 32.83 ± 6.45 and 31.03 ± 6.14, respectively. Due to the normality of data distribution using independent t-test between age variables in karyotype and GCH groups, there was a significant relationship between two groups and age variables (p=0.02). In terms of the number of gravities in both groups, the highest frequency was related to the number of gravities one and two with 40 (31.3%) and 39 (32.8%) in the karyotype and GCH groups, respectively. While the lowest frequency of gravities in both groups was related to the number of gravities five with a frequency of 2 (1.7%) in the GCH group and 4 (3.1%) in the karyotype group. In general, our results showed there was no statistically significant relationship between the number of gravities in two groups (p=0.95) (Table 1).

In terms of number of parities, 47 (39.5%) in GCH group and 46 (35.9%) in the karyotype group had no parity. On the other hand, 40 (33.6%) and 45 (35.2%) had one parity in the karyotype and GCH groups, respectively. The lowest number of parities in both groups was related to the number of 4 parity with frequency 1 (0.8%) in the GCH group and 43 (2.3%) in the karyotype group. The result of Chi-square test indicated that there was no statistically significant relationship between the number of parities between two groups (p=0.088).

Also, no abortion history was reported in 93 cases (39.5%) and 101 cases (78.9%) in the karyotype and GCH groups, respectively. While in 21 cases (33.6%) in the karyotype group and 24 cases (18.8%) in the GCH group, there was a history of one abortion. The results revealed that there was no statistically significant relationship between the number of abortions in both groups (p=0.7).

Table 2 shows the results of sample analysis in two groups. In the present study, the total number of cases was 247 with 128 cases in the karyotype group and 119 cases in the CGH group. 116 samples (90.6%) in the karyotype group and 99 samples (83.2%) in the CGH group showed normal karyotype. 4.2% (5 samples) of chromosomal abnormalities in the CGH group displayed trisomy while in the karyotype group 7.9% (10 samples) was trisomy. The results of karyotypes related to other chromosomal abnormalities in two groups is shown in Table 2. In the present study, CGH array analysis on chromosomal abnormalities showed copy number variation (CNV) in about 9.2% (11 samples) of cases that was not observed by karyotype analysis. The frequency of syndromes diagnosed only by CGH is shown in Table 3.

**Risk factors structural chromosomal in the Karyotype and GCH groups**

Frequency and percent risk factors structural chromosomal in two groups is presented in Table 4. A statistically significant relationship was observed in term of history of disabled children in family, maternal age, history of anomalies, screening of the first trimester of pregnancy, and increased NT (p<0.05).

In the karyotype group, 121(95%) samples were CVS and 7 (5%) samples were AC, while there were 161 (96%) and 9 (4%) samples were CVS and AC, respectively. There was no statistically significant relationship between the type of sampling in the karyotypes and GCH groups (p=0.4)

**Discussion**

The current method of prenatal diagnosis of chromosomal abnormalities was non-invasive evaluation of trisomy 21 and other aneuploidy risk in the first trimester of pregnancy, or comprehensive risk screening for all pregnant women ([14](#_ENREF_14)). If these screening methods are at high risk, standard chromosomal analysis after chorionic villus sampling (CVS) or amniocentesis (AC) is recommended to detect numerical or structural chromosomal abnormalities ([15](#_ENREF_15)). However, in clinical practice, pregnant women with high risk of aneuploidy for a variety of reasons often show normal chromosomal analysis ([16](#_ENREF_16)). The restricted clinical data provided by ultrasound imaging of fetal anatomy and physical progress cannot confirm the diagnosis of a particular disease with a specific test, leaving parents with the risk of developing a developmental delay and / or accepting a high-risk condition with unknown details ([17](#_ENREF_17)). Array comparative genomic hybridization (aCGH), which can offer higher resolution than conventional karyotyping, is now the first choice genetic test for prenatal study of intellectual disability (ID) and/ or multiple congenital abnormalities (MCA) ([18](#_ENREF_18)). However, important questions about the appropriate platform and clinical practice resolution remain unanswered ([19](#_ENREF_19), [20](#_ENREF_20)). Significant advances in previous screening and diagnostic testing of genetic disorders have shifted prenatal diagnosis to the second trimester before diagnosis ([21](#_ENREF_21)). In the experimental third ultrasound centers, the detection rate of fetal structural abnormalities in the first trimester ultrasound is as high as 40%. Since the purpose of the first trimester screening is to provide an initial diagnosis, we considered the chorionic villi sample to be an invasive method of selection ([22](#_ENREF_22)). Row-based methods have the ability to considerably decrease turnout time and quickly change testing via the interface FISH, QF-PCR, or MLPA ([23](#_ENREF_23)).  CGH on chorionic villi can provide time-saving and preliminary approaches for comprehensive and high-resolution diagnosis of chromosomal abnormalities after the first trimester risk screening ([24](#_ENREF_24)). In our experience, CGH was an important diagnostic test. The CGH test is a potent test for fetal abnormalities in the pre-selected high-risk populations and a suitable way to detect autosomal mosaic trisomy that is not covered by PCR ([25](#_ENREF_25)). Though, it is difficult to assess the degree of mosaicism in the fetus because of the deterioration of cell culture. Once this technique became accessible in the laboratory, the CGH array soon became part of the clinical program ([26](#_ENREF_26)). Parental samples are usually analyzed with fetal samples, which is necessary to get timely final conclusions for the possibility of making fact-based decisions about pregnancy ([27](#_ENREF_27)). In our study, it was found that there was a significant increase in the power of detection by CGH-array and karyotype, regardless of the age of the mother, the history of the disabled child anomalies (Table 3-1). Our results also showed that the detection power of CGH in the diagnosis of chromosomal abnormalities was 9.2% that in 6 cases (5%) was related to deletion and in 5 cases (4.2%) was related to duplication. For risk factors for chromosomal composition in syndromes diagnosed solely by CGH, most risk factors were increased NT history and history of disabled children in family. In the present study, clinical indications CGH invasive prenatal testing enhanced the risk of nuclear translucency (> 3 mm) and / or high risk first trimester screening. A recent study evaluated on 4 pathogenic submicroscopic abnormalities and used custom designed arrays with a nuclear translucency of more than 3.5 mm at an average resolution of 100 KB in the range of 1.2 mm to 7.9 MB. Nevertheless, 2 of these fetuses had additional sonographic abnormalities ([28](#_ENREF_28)). The CGH procedure solution may be an effective method in diagnosing of CNV in unknown medical significance ([28](#_ENREF_28)). It has been found that there is a large group of embryos with distinct enhanced nuchal translucency. In a recent study, pathogen copy number changes were detected in only 2.7% of euploid fetuses with a nuchal translucency incidence of ≥ 3.5 mm (n ¼ 16) and approximately half of them had CNV with neurodevelopmental disorders (n ¼ 7). Besides, CNV was identified in 13.7 of the embryos with increased nuchal translucency (N ¼ 15). But, aneuploids were included in this number due to failure or delay in PCR testing (including one case of trisomy 21, 1 case of complete X monosomy and 3 cases of X monosomal mosaicism) and the actual percentage of pathogenic CNVs in oploid embryos. It was 9.2%, which included 2 cases of 22q11.2 deletion, 1 case of feline eye syndrome, 1 case of unbalanced chromosomal displacement, and 2 cases with more than one pathogen CNV ([29](#_ENREF_29)).

In a group, of 4282 embryos, diagnostic performance was 6% in samples with normal fetal karyotype and structural abnormalities, and 1.7% had positive screening results in cases of advanced maternal age ([30](#_ENREF_30)). In addition, there was the diagnostic yield of 4.2% in the group of 1,075 preterm fetuses without known chromosomal abnormalities or familial genomic imbalances ([31](#_ENREF_31)).

Pregnant women under the age of 36 appeared to have a higher prevalence of submicroscopic disease than trisomy 21 during invasive testing, which may be due to maternal age or maternal anxiety ([32](#_ENREF_32)). In a study, 39 fetuses with 2 or more abnormalities in the cardiovascular, urinary, skeletal, and gastrointestinal systems or central nervous system were diagnosed with CGH after birth. Thirty-seven of them had normal karyotypes, and two had unbalanced karyotypes that could not be detected by conventional cytogenetic methods. Two unbalanced karyotypes were identified by CGH array, and four additional abnormalities were identified, an unbalanced translocation, band deletion, q11.222 deletion, p361, and a .6p12.1-21.2 amplification at the end of chromosomal imbalance at 6 m 39.4 The embryo was identified and showed the importance of the CGH array routinely in cases with multiple inherited disorders as well as unspecified chromosomal rearrangements ([33](#_ENREF_33)).

Besides, a study illustrated that the CGH array was able to detect aneuploidy in DNA collected from at least 1 ml of uncultured amniotic fluid. 29.30 samples were appropriately identified, with the exclusion of one case of triploidy ([34](#_ENREF_34)).

Schaeffer et al. used DNA arrays containing genomic clones for each telomere to analyze 41 karyotyped samples. They concluded that the CGH array could identify all abnormalities formerly detected by microscopic karyotype analysis, as well as further abnormalities. The CGH-array DNA overcomes many limitations of routine cytogenetic analysis and increases the detection of fetal chromosomal abnormalities ([35](#_ENREF_35)).

In the present study in the CGH group, patients showed increased nuchal translucency and an increased NT history, while the ratio of fetuses to congenital anomalies was relatively low. Our findings are consistent with the results of Faas et al., who showed an increase in nuchal translucency in 95 fetal samples with ultrasound abnormalities when performed a strategy to detect a typical array parallel to the QFPCR. Thus, high-resolution genome arrays might be particularly effective in pregnancies with diverse fetal ultrasound abnormalities or in the accurate determination of rare structural chromosomal abnormalities. Our method with a detection rate of 11.2% for CNVs of unknown importance in a given resolution demonstrated that aCGH seems to be a reliable way to diagnose the first trimester pregnancies in women with high risk for chromosomes abnormalities ([36](#_ENREF_36)). In our experience, aCGH was technically reliable as a first-line diagnostic test for prenatal specimens, substituting the laborious direct CVS preparation, as well as other rapid but fewer extensive testing procedures. Consequently, aCGH offers the benefit of providing patients with a further complete genome ([37](#_ENREF_37), [38](#_ENREF_38)). The finding of our analysis was for a short period of time. Higher resolution matrices may become more important, as we can believe that the clinical use of non-invasive diagnostics for common aneuploidies can enhance the percentage of high-risk pregnancy samples achieved by invasive diagnosis. Nonetheless, the suitable resolution of the matrix remains a matter of debate and may requirement to be tailored to the specific clinical indication and / or parental expectations ([39](#_ENREF_39), [40](#_ENREF_40)).

**Conclusion**

High-resolution arrays may specially prevent fetal malformations. Until now, normal prenatal chromosome analysis has been shown a relative standard method, but CGH may be helpful to specialists in diagnosing chromosomal abnormalities, especially in unknown chromosomal abnormalities.

**Declarations**

**Authors’ contributions**

S. M. and E. SH. have made contributions to the writing of the manuscript. F. M. and N. S. have made contributions to the design of the tables and the revision of the manuscript. M. B. and E. SH. have made contribution to the analysis of the data. All authors have approved the submitted version of the article and have agreed to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. All authors read and approved the final manuscript.

**Funding**

Not applicable**.**

**Availability of data and materials**

**The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.**

**Ethics approval and consent to participate**

**Not applicable.**

**Consent for publication**

**Not applicable**

**Competing interests**

The authors declare that there is no competing interests.

**Acknowledgements**

**Not applicable**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 1. Descriptive statistics of study variables** | | | | |
| Variable | | karyotype | CGH | p-value |
| Frequency (percent) | Frequency (percent) | 0.95 |
| Number of gravities | 1 | (31.3)40 | (32.8)39 |
| 2 | (31.3)40 | (32.8)39 |
| 3 | (21.9)28 | (21)25 |
| 4 | (12.5)16 | (11.8)14 |
| 5 | (3.1)4 | (1.7)2 |
| parity | 0 | (35.9)46 | (39.5)47 | 0.88 |
| 1 | (35.2)45 | (33.6)40 |
| 2 | (22.7)29 | (21.8)26 |
| 3 | (3.9)5 | (4.2) 5 |
| 4 | (2.3)3 | (0.8) 1 |
| Number of abortions | 0 | (78.9)101 | (39.5)93 | 0.7 |
| 1 | (18.8)24 | (33.6)21 |
| 2 | (22.7)3 | (21.8)5 |
| Age (mean±SD) | | 32.83 ± 6.45 | 31.03 ± 6.14 | 0.02 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2. The results of sample analysis in two groups** | | | |
| **Chromosomal abnormalities** | **karyotype** | **GCH** | **p-value** |
| **Frequency (percent)** | **Frequency (percent)** | 0.005 |
| 45 XO/turners |  |  |
| 47 xxxx |  |  |
| Deletion of ch |  |  |
| Down syndrome (Trisomy 21) |  |  |
| Duplication |  |  |
| Edward syndrom |  |  |
| Jacob syndrom |  |  |
| Normal |  |  |
| Total | 128 | 119 |  |

|  |  |  |
| --- | --- | --- |
| **Table 3. The frequency of syndromes diagnosed only by CGH** | | |
| **CGH** | **Frequency** | **Percent** |
| Deletion of ch | 3 | 2.5 |
| Di-george | 1 | 0.8 |
| Duplication | 4 | 3.4 |
| Micro-deletion | 2 | 1.7 |
| Williams syndrome | 1 | 0.8 |
| Total | 11 | 9.2 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **3.1. Risk factors structural chromosomal in the Karyotype and GCH groups** | | | | |
|  | | karyotype | GCH | p-value |
| Frequency (percent) | Frequency (percent) |  |
| Disabled children | No | (98.6)126 | (84)100 |
| Yes | (1.6)2 | (16)19 |
| Twin children | No | (96.9)124 | (94.1)112 | 0.29 |
| Yes | (3.1) 4 | (5.9)7 |
| Old age of the mother | No | (88.3)113 | (99.2)118 | 0.001 |
| Yes | (11.7) 15 | (0.8)1 |
| History of trisomy | No | (100)128 | (92.4)110 | 0.002 |
| Yes | 0 (0) | (7.6) 9 |
| History of anomalies | Yes | (93.8)120 | (76.5) 91 | <0.001 |
| No | (6.3)8 | (23.5)28 |
| Screening of the first trimester of pregnancy | Yes | (70)90 | (84)118 | 0.8 |
| No | (30)38 | (0.8)1 |
| Mental retardation | Yes | (72)91 | (46.2)55 | 0.7 |
| No | (28) 37 | (53.8)64 |
| Nuchal translucency test (NT) | Yes | (70) 90 | (84)118 | 0.6 |
| No | (30)38 | (0.8)52 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 4. Copy number variants of unknown significance in the CGH group** | | | |
| **Type of aberration** | **Chromosomal region/ Maximal size of aberration** | **Risk factors structural chromosomal** | **Clinical finding** |
| Duplication | Duplication of Chromosome 22  (2.6 Mb) | Screening of the first trimester of pregnancy | Muscle Hypotonia  Delayed Speech  Intellectual Disability |
| Deletion | Deletion of Chromosome 7q  (301 Kb) | Increased nuchal translucency (NT) | No Clinical finding |
| Deletion | Deletion of Chromosome 12  (5.6 Mb) | History of anomalies | Growth Retardation  Developmental Delay  Intellectual Disability |
| Deletion | Deletion of Chromosome 17q 12  (133 Kb) | History of anomalies | Development Delay  Muscle Hypotonia  Microcephaly  Intellectual Disability |
| Duplication | Duplication of Chromosome 3q  (56.7 Mb) | Increased nuchal translucency (NT) | Multiple Congenital Anomalies |
| Deletion | Deletion of Chromosome 3p 25  (5.6 Mb) | Increased nuchal translucency (NT) | Multiple Congenital Anomalies |
| Deletion | Deletion of Chromosome 17q 12, (1.26 Mb) | Child with myelomeningocele | - |
| Deletion | Deletion of Chromosome 17q 1  (5.6 Mb) | Increased nuchal translucency (NT) | Microcephaly |
| Duplication | Duplication of Chromosome 1q 21.1  (258 Kb) | Increased nuchal translucency (NT) | Abnormality of Metatarsal Bone  Skin Aplasia |
| Deletion | Chromosome 17q11.23  Deletion syndrome 1.8 Mb  (William syndrome) | Increased nuchal translucency (NT) | Developmental disorder |
| Deletion | 22q11.2 Deletion syndrome  (3 Mb) | Screening of the first trimester of pregnancy | Multiple Congenital Anomalies |

**References**

1. Prescott KR, Wilkie AOM. Genetic aspects of birth defects: new understandings of old problems. Arch Dis Child Fetal Neonatal Ed. 2007;92(4):F308-F14.

2. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Advances in experimental medicine and biology. 2010;686:349-64.

3. Norwitz ER, Levy B. Noninvasive prenatal testing: the future is now. Rev Obstet Gynecol. 2013;6(2):48-62.

4. Carlson LM, Vora NL. Prenatal Diagnosis: Screening and Diagnostic Tools. Obstet Gynecol Clin North Am. 2017;44(2):245-56.

5. Rickman L, Fiegler H, Shaw-Smith C, Nash R, Cirigliano V, Voglino G, et al. Prenatal detection of unbalanced chromosomal rearrangements by array CGH. J Med Genet. 2006;43(4):353-61.

6. Hyde KJ, Schust DJ. Genetic considerations in recurrent pregnancy loss. Cold Spring Harb Perspect Med. 2015;5(3):a023119-a.

7. Benchikh S, Bousfiha A, Razoki L, Aboulfaraj J, Zarouf L, Elbakay C, et al. Chromosome Abnormalities Related to Reproductive and Sexual Development Disorders: A 5-Year Retrospective Study. BioMed Research International. 2021;2021:8893467.

8. Rickman L, Fiegler H, Shaw-Smith C, Nash R, Cirigliano V, Voglino G, et al. Prenatal detection of unbalanced chromosomal rearrangements by array CGH. J Med Genet. 2006;43:353-61.

9. Grimshaw G, Szczepura A, Hulten M, MacDonald F, Nevin N, Sutton F, et al. Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities. Health technology assessment (Winchester, England). 2003;7(10):1-146.

10. Pös O, Radvanszky J, Styk J, Pös Z, Buglyó G, Kajsik M, et al. Copy number variation: methods and clinical applications. Applied Sciences. 2021;11(2):819.

11. Das RR, Natarajan SG, Agrawal SS, Bhattacharya IP. TOWARDS ANALYSING COMPARATIVE GENOMIC HYBRIDISATION METHOD. Journal of Advanced Scientific Research. 2020;11.

12. Traversa MV, Marshall J, McArthur S, Leigh D. The genetic screening of preimplantation embryos by comparative genomic hybridisation. Reproductive biology. 2011;11 Suppl 3:51-60.

13. Kleeman L, Bianchi DW, Shaffer LG, Rorem E, Cowan J, Craigo SD, et al. Use of array comparative genomic hybridization for prenatal diagnosis of fetuses with sonographic anomalies and normal metaphase karyotype. Prenat Diagn. 2009;29(13):1213-7.

14. Health Quality O. Noninvasive Prenatal Testing for Trisomies 21, 18, and 13, Sex Chromosome Aneuploidies, and Microdeletions: A Health Technology Assessment. Ont Health Technol Assess Ser. 2019;19(4):1-166.

15. Alfirevic Z, Sundberg K, Brigham S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev. 2003(3):CD003252-CD.

16. Driscoll DA, Gross SJ, Professional Practice Guidelines C. Screening for fetal aneuploidy and neural tube defects. Genet Med. 2009;11(11):818-21.

17. Wojcik MH, Reimers R, Poorvu T, Agrawal PB. Genetic diagnosis in the fetus. Journal of Perinatology. 2020;40(7):997-1006.

18. Vallespin E, palomares bralo M, Mori M, Martin R, García-Miñaúr S, Fernandez L, et al. Customized High Resolution CGH-Array for Clinical Diagnosis Reveals Additional Genomic Imbalances in Previous Well-Defined Pathological Samples. American journal of medical genetics Part A. 2013;161.

19. Watson CT, Marques-Bonet T, Sharp AJ, Mefford HC. The genetics of microdeletion and microduplication syndromes: an update. Annu Rev Genomics Hum Genet. 2014;15:215-44.

20. Freitas M, Pinto J, Ramalho C, Dória S. Prenatal diagnosis: the clinical usefulness of array comparative genomic hybridization. Porto Biomedical Journal. 2018;3(2).

21. Van den Veyver IB. Recent advances in prenatal genetic screening and testing. F1000Res. 2016;5:2591-.

22. Wilson RD, Gagnon A, Audibert F, Campagnolo C, Carroll J, Brock J-A, et al. Prenatal diagnosis procedures and techniques to obtain a diagnostic fetal specimen or tissue: maternal and fetal risks and benefits. Journal of Obstetrics and Gynaecology Canada. 2015;37(7):656-68.

23. Isidori I, Spapperi C, Barbati A, Mencarelli A, Stangoni G. QF-PCR and MLPA: a reliable molecular system to detect chromosomal alterations in miscarriages. Clinical and experimental obstetrics & gynecology. 2017;44(2):220-5.

24. Lichtenbelt K, Knoers N, Schuring-Blom G. From karyotyping to array-CGH in prenatal diagnosis. Cytogenetic and genome research. 2011;135(3-4):241-50.

25. Evangelidou P, Alexandrou A, Moutafi M, Ioannides M, Antoniou P, Koumbaris G, et al. Implementation of high resolution whole genome array CGH in the prenatal clinical setting: advantages, challenges, and review of the literature. BioMed research international. 2013;2013:346762-.

26. Meza-Zepeda LA, Noer A, Dahl JA, Micci F, Myklebost O, Collas P. High-resolution analysis of genetic stability of human adipose tissue stem cells cultured to senescence. J Cell Mol Med. 2008;12(2):553-63.

27. Blakeley C, Smith DM, Johnstone ED, Wittkowski A. Parental decision-making following a prenatal diagnosis that is lethal, life-limiting, or has long term implications for the future child and family: a meta-synthesis of qualitative literature. BMC Med Ethics. 2019;20(1):56-.

28. Leung T, Vogel I, Lau T, Chong W, Hyett J, Petersen O, et al. Identification of submicroscopic chromosomal aberrations in fetuses with increased nuchal translucency and apparently normal karyotype. Ultrasound in obstetrics & gynecology. 2011;38(3):314-9.

29. Egloff M, Hervé B, Quibel T, Jaillard S, Le Bouar G, Uguen K, et al. Diagnostic yield of chromosomal microarray analysis in fetuses with isolated increased nuchal translucency: a French multicenter study. 2018;52(6):715-21.

30. Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. The New England journal of medicine. 2012;367(23):2175-84.

31. Breman A, Pursley AN, Hixson P, Bi W, Ward P, Bacino CA, et al. Prenatal chromosomal microarray analysis in a diagnostic laboratory; experience with> 1000 cases and review of the literature. Prenatal diagnosis. 2012;32(4):351-61.

32. Srebniak MI, Joosten M, Knapen M, Arends LR, Polak M, van Veen S, et al. Frequency of submicroscopic chromosomal aberrations in pregnancies without increased risk for structural chromosomal aberrations: systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018;51(4):445-52.

33. Vialard F, Gomes DM, Leroy B, Quarello E, Escalona A, Le Sciellour C, et al. Array comparative genomic hybridization in prenatal diagnosis: another experience. Fetal diagnosis and therapy. 2009;25(2):277-84.

34. Rickman L, Fiegler H, Shaw-Smith C, Nash R, Cirigliano V, Voglino G, et al. Prenatal detection of unbalanced chromosomal rearrangements by array CGH. J Med Genet. 2006;43(4):353-61.

35. Schaeffer AJ, Chung J, Heretis K, Wong A, Ledbetter DH, Lese Martin C. Comparative genomic hybridization-array analysis enhances the detection of aneuploidies and submicroscopic imbalances in spontaneous miscarriages. Am J Hum Genet. 2004;74(6):1168-74.

36. Evangelidou P, Sismani C, Ioannides M, Christodoulou C, Koumbaris G, Kallikas I, et al. Clinical application of whole-genome array CGH during prenatal diagnosis: Study of 25 selected pregnancies with abnormal ultrasound findings or apparently balanced structural aberrations. Mol Cytogenet. 2010;3:24-.

37. Miny P, Wenzel F, Tercanli S, Filges I. Chromosomal microarrays in prenatal diagnosis: time for a change of policy? Microarrays. 2013;2(4):304-17.

38. Filges I, Kang A, Klug V, Wenzel F, Heinimann K, Tercanli S, et al. Array comparative genomic hybridization in prenatal diagnosis of first trimester pregnancies at high risk for chromosomal anomalies. Mol Cytogenet. 2012;5:38.

39. Qi G, Yi J, Han B, Liu H, Guo W, Shi C, et al. Noninvasive prenatal testing in routine clinical practice for a high-risk population: Experience from a center. Medicine (Baltimore). 2016;95(41):e5126-e.

40. Nepomnyashchaya YN, Artemov AV, Roumiantsev SA, Roumyantsev AG, Zhavoronkov A. Non-invasive prenatal diagnostics of aneuploidy using next-generation DNA sequencing technologies, and clinical considerations. Clinical chemistry and laboratory medicine. 2013;51(6):1141-54.