




ORIGINAL ARTICLE

Chromosomal aberrations in pregnancy and fetal loss: Insight on the effect of consanguinity, review of 1625 cases

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Abstract

Background: Pregnancy loss affects 10%–15% of pregnancies and is caused by several factors, maternal and fetal. Most common cause is chromosomal aneuploidy and has traditionally been detected by karyotyping product of conception and/or fetal tissue. In recent years, array comparative genomic hybridization (a-CGH) has been used because of its higher detection and lower failure rates.

Methods: DNA was extracted from 1625 products of abortion or fetal tissue. In 1,104 cases both quantitative fluorescent-polymerase chain reaction (QF-PCR) and a-CGH, and in 521 cases only a-CGH, was performed.

Results: The detection rate using QF-PCR and a-CGH is 20% compared to 12.7%, overall, and 15.7%, excluding failed samples, by karyotypes in our center. QF-PCR and a-CGH failed in 1.9% of cases, while the failure rate for karyotypes was 20.1%. The difference of detection and failure rates is significant (p -value < 0.001 and p -value < 0.001 respectively). Unexpectedly we also found a significant difference in frequency of imbalances in related versus unrelated couples. ($\chi^2 = 11.4926$, p -value < 0.001).

Conclusion: It is highly likely that the pregnancy loss in consanguineous couples is caused by other genetic and immune mechanisms. It is plausible that, through the same mechanism by which single gene disorders have a higher prevalence of manifesting disease in consanguineous couples, they can cause lethal genetic disorders leading to pregnancy loss and intra-uterine fetal death (IUID) in these couples. Our findings suggest that this is a matter for further study as it will greatly influence the approach to counseling and managing consanguineous couples with pregnancy loss.

KEYWORDS

array comparative genomic hybridization, chromosomal abnormality, consanguinity, miscarriage, recurrent abortion

1 | INTRODUCTION

Miscarriage or pregnancy loss (PL) is the spontaneous loss of an embryo or fetus within the first 20 weeks (MacDorman & Gregory, 2015; Zhang et al., 2009) affecting 10%–15% of pregnancies (Schaeffer et al., 2004). Most miscarriages occur in the first trimester (under 13 weeks) (MacDorman & Gregory, 2015; Zhang et al., 2009). Recurrent pregnancy loss is defined as two or more pregnancy losses (Practice Committee of the American Society for Reproductive Medicine, 2012) and affects 3–5 percent of couples (Rajcan-Separovic et al., 2010; Stephenson & Kutteh, 2007).

Pregnancy and fetal loss is caused by many factors, some of which are maternal such as TORCH infections, hypothyroidism, diabetes, uterine anatomical abnormalities and etc. Other causes are fetal and some are the result of immune reactions between fetus and mother. The most common fetal cause of pregnancy loss is considered to be chromosomal abnormalities, accounting for half of first trimester and one third of second trimester losses (Godijn & Leschot, 2000; Zhang et al., 2009). To date, we have no study of the possible effect, if any, of consanguinity on pregnancy loss and intra-uterine fetal death (IUFD).

Traditionally chromosomal analysis of product of conception by karyotyping has been the routine test, which has major limitations including its need for viable tissue, culture failure rates (10%–40%) (Donaghue et al., 2017; Lomax et al., 2000; Schaeffer et al., 2004), maternal cell contamination (Bell, Van Deerlin, Haddad, & Feinberg, 1999; Robberecht, Schuddinck, Fryns, & Vermeesch, 2009; Schaeffer et al., 2004), and resolution (usually below 5–10 Mb).

Recently with the advent of new technologies comparative genomic hybridization (CGH) and subsequently array based comparative genomic hybridization (a-CGH) of DNA extracted from uncultured or paraffin-embedded product of conception/fetal tissue has become a more accurate and objective alternative for the detection of fetal chromosome anomalies (Bell, Van Deerlin, Feinberg, du Manoir, & Haddad, 2001; Daniely, Aviram-Goldring, Barkai, & Goldman, 1998; Fritz et al., 2001; Rosenfeld et al., 2015; Tabet et al., 2001). Among the many advantages of this technique is the use of DNA instead of metaphase spreads, which makes study of more samples possible, its objectivity and reproducibility, and its higher resolution (Robberecht et al., 2009).

The major limitation of this technique, is its inability to detect polyploidy, low grade mosaicism and balanced rearrangements (Schaeffer et al., 2004). Whereas, balanced rearrangements and low-grade mosaicism are unlikely causes of pregnancy loss, polyploidy accounts for 8%–15% (Jia et al., 2015; Wou et al., 2016).

To overcome the major limitations of the technique for the study of products of conception, from 2010 in our center, we have replaced G-banded karyotyping with quantitative

fluorescence- polymerase chain reaction (QF-PCR) and a-CGH.

We are reporting the results of our 7-year experience and a comparison of the results from a-CGH with our 20-year experience with karyotyping. In addition, we are comparing the rate and frequency of chromosomal aberrations in consanguineous couples with nonconsanguineous couples.

2 | MATERIALS AND METHODS

From October 2010 till May 2018, we have performed a-CGH, QF-PCR and fetal autopsy, where applicable, on the product of pregnancy, to all couples referred to Kariminejad - Najmabadi Pathology & Genetics center. During a counseling session, clinical history and a pedigree were recorded for all couples and where applicable an inbreeding coefficient was calculated. Couples were asked to sign an informed consent for the tests and the inclusion of results and samples in research. As we are a national referral center, 521 of the cases were referred by other laboratories for a-CGH, and QF-PCR was not performed by us and for which the results are not available. (Figure S1).

All samples of products of conception were initially screened under the microscope and chorionic villi were selected and cleansed of maternal cells. Maternal blood was also requested for analysis of maternal cell contamination by STR fingerprinting (20); those samples testing positive for maternal cell contamination were excluded from this study. All fetal specimens were biopsied, usually from the quadriceps.

Follow-up study including oligo array and/or FISH of parents for unknown CNVs, pathogenic CNVs, deletions/duplications with possible risk of recurrence, were conducted and the results were explained to the couples during another counseling session.

Prior to 2010, 1772 product of conception and fetal samples had been karyotyped. Two cultures were set up on the samples obtained from products of conception or fetal tissue. When possible 20 metaphase spreads were studied with equal distribution between the two cultures and two karyotypes prepared.

2.1 | DNA extraction

DNA was extracted from product of conception/fetal biopsy, and maternal blood (for first trimester cases) using salting out method (Miller, Dykes, & Polesky, 1988). Concentration and quality of the extracted DNA were measured with the NanoDrop spectrophotometer (NanoDrop Technologies, Inc.). DNA with optical density of less than 100 µg/ml, 260/230, and 260/280 less than 1.5 was excluded.

2.2 | QF-PCR

QF-PCR was performed using different highly polymorphic STRs markers for chromosome 13, 18, 21, X, and Y (Cirigliano et al., 2001). A total of five STRs on each chromosome 13, 18, and 21, one STR on chromosome X, four for pseudo autosomal regions and one on chromosome Y were selected.

5 μ L of the extracted DNA was applied in two multiplex PCR reactions using Aneufast QF-PCR kit (Aneufast Multiplex QF-PCR kit, Switzerland). Products were analyzed using the ABI3130 (Applied Biosystems, Foster City, CA) and Gene Mapper v.4 software (Student, 2015).

2.3 | BAC Array CGH

Initially from 2010 to 2011 107 of samples were studied using CYTOCHIP genomic BAC array version 3.0 and data were analyzed using BlueFuse Multi software. BAC array CGH was performed using 400 ng DNA following manufacturer's protocol. (Blugnome, Cambridge).

2.4 | Oligo array CGH

From late 2011 to May 2018 oligo array CGH (oa-CGH) was performed on 1518 samples using CYTOCHIP 4X44 and later 8X60 whole genome oligo array according to manufacturer's protocol. (Blugnome, Cambridge, Agilent Technologies, Düsseldorf-Ratingen).

2.5 | Data analysis

All samples were hybridized on a patient-patient basis and ownership of copy number variations (CNVs) was determined using signal intensities (Donaghue et al., 2017).

CNVs were screened against Database of Genomic Variants, and the common polymorphic regions were excluded. In addition, we screened the findings against our

patient database and discarded the variants present in our database with frequency equal to or exceeding 1%.

Due to the lack of clinical information in most cases (no autopsy) we have screened all CNVs according to size and disregarded all findings that were under 1 Mb in size. Only those smaller CNVs were considered that involved known pathogenic variations that have correlating disabling phenotypes, or were present in homozygous pattern (Kearney, Thorland, Brown, Quintero-Rivera, & South, 2011).

2.6 | Statistical analysis

Chi-square test, Mann–Whitney, Kruskal–Wallis test Spearman correlation test and Kendell Correlation, was used to investigate whether distributions of variables differ from one another specifically for pathogenic findings across trimesters and consanguinity, recurrent abortion and consanguinity and karyotype results versus QF-PCR and a-CGH.

2.7 | Ethical Approval

This study was conducted in compliance with Helsinki Declaration. All patients signed consent forms after a session of consultation.

3 | RESULTS

Total of 1625 samples were referred following pregnancy loss and IUFD. Trimester was determined by gestational age, under or equal to 13 weeks was considered first, 14–26 weeks as second and over 26 weeks as third. The inbreeding with inbreeding coefficients in consanguineous couples were between $F = 0.125$ to $F = 0.0156$. In Table 1, we have ordered the samples are by trimester, couples relation and former history of pregnancy loss and IUFD.

Most of the cases were referred in the second trimester (45.4%) compared to 40.4% in first and 14.2% in third

TABLE 1 Sample frequencies by trimester, consanguinity, and number of abortion

	Trimester			Total
	First	Second	Third	
	656(40.4%)	738(45.4%)	231(14.2%)	
Consanguineous				
Yes	199	268	94	561(34.5%)
No	388	405	113	906(55.8%)
Unknown	69	65	24	158(9.7%)
Recurrent abortion				
Yes	442	359	82	883(54.3%)
No	158	314	126	598(36.8%)
Unknown	56	65	23	144(8.9%)

trimesters. The majority of cases were referred following recurrent abortion and/or IUFD (54.3%).

Positive correlation of consanguinity and recurrent abortion was tested with Kendall correlation test and was approved (Correlation Coefficient 0.294, Sig 0.000). However, there was no significant correlation between number of abortions and consanguinity. (Tested with Spearman correlation, Sig 0.385, Correlation Coefficient – 0.023).

Test failed in 1.9% of cases because of sample degradation and/or poor DNA quality, ($n = 30$) while the failure rate for karyotypes was 20.1% Figure 1.

Detection rate using QF-PCR and a-CGH is 20% compared to 12.7% overall and 15.7% excluding failed samples by karyotypes in our center. The difference of detection rate and failure rate is significant, (tested with Chi-Square test $\chi^2 = 31.4538$, p -value = 0.0000 and $\chi^2 = 280.5421$, p -value = 0.0000).

In 69.2% of cases ($n = 1,104$) QF-PCR was initially performed, followed by a-CGH in case of normal results. In the remaining 30.8% only a-CGH was performed following initial screening in the referring laboratory. This would suggest that all cases with numerical chromosomal abnormalities of chromosomes 13, 18, 21 were excluded. Detected abnormalities are shown in Figure 2, and have been divided as those detectable by QF-PCR only (such as polyploidy), by a-CGH (aberrations of chromosomes other than X, Y, 13, 18, 21) or by both techniques (chromosomes X, Y, 13, 18, 21).

Of 319 abnormal cases, 46% ($n = 147$) had numerical abnormalities of the five chromosomes 13, 18, 21, X, and Y, 18% ($n = 56$) had numerical abnormalities of other chromosomes, 16% ($n = 50$) had polyploidies, 15% ($n = 48$) had deletion or duplication, 4% ($n = 14$) had unbalanced translocation, and 1% ($n = 4$) were mole. Of the 48 cases with partial deletion or duplication, 12 were over 10 Mb, 26 were 1–10 Mb and 10 were under 1 Mb in size. (Figure 3) In supplementary tables

I and II, imbalances over 1 Mb and less than 1 Mb are shown respectively.

We calculated the detection rate of our method in the three trimesters (Figure 4). We divided the detection rate in each trimester by consanguinity (Figure S2). We have the highest rate of aberrations in the first trimester (31.8%) and the lowest in the third trimester (8.26%). In each trimester the detection rate in unrelated couples is higher. The difference between the rates of abnormality in the trimesters is significant (Kruskal-Wallis $\chi^2 = 98.371$, Sig = 0.000). In Figure 5 abnormalities detected are shown in each trimester.

Around 94% of abnormalities detected by a-CGH are de novo. In Figure 6 we compare the frequency of imbalances in related versus unrelated couples and the difference is statistically significant. ($\chi^2 = 11.4926$, p -value = 0.0006, Mann-Whitney 229,029, Sig = 0.001, $Z = -3.307$).

4 | DISCUSSION

The combination of A-CGH and QF-PCR is a very efficient technique for the detection of chromosome abnormalities in abortion and stillbirth. Detection of the cause of abortion/IUFD is important in the management of a couple's future pregnancies. It has been established that chromosomal aberrations are the main single cause of pregnancy loss, especially in the first trimester. Recent reports have used a-CGH (Bagheri, Mercier, Qiao, Stephenson, & Rajcan-Separovic, 2015; Borovik et al., 2008; Dhillon et al., 2014; Donaghue et al., 2017; Ozawa et al., 2016; Rajcan-Separovic et al., 2010, 2009; Schaeffer et al., 2004; Wou et al., 2016) for detection of cause of abortion. Although a-CGH has high resolution, it has its limitations. Polyploidy which is a major cause of abortion in the first trimester 8%–15% is usually missed in A-CGH (Jia et al., 2015; Wou et al., 2016). Wou et al suggested a protocol including QF-PCR for diagnosis of abortion (Wou et al., 2016). The application of QF-PCR has the added benefit of providing information for determination of maternal cell contamination of the DNA when compared with maternal DNA. We believe that the use of a combination of the two techniques QF-PCR and a-CGH is a more effective method for the detection of chromosomal aberrations than karyotyping.

Our failure rates using QF-PCR and a-CGH in comparison to karyotyping have decreased from 20% to less than 2% and our detection rate has risen from 12.7% to 20% overall. The ability to detect smaller abnormalities is evident in the fact that 36 copy number variations that are beyond the resolution of karyotyping were detected by a-CGH and the 4 moles that would appear as normal karyotype were detected by QF-PCR.

When comparing our detection rate with other previous studies, we find lower incidence of chromosomal

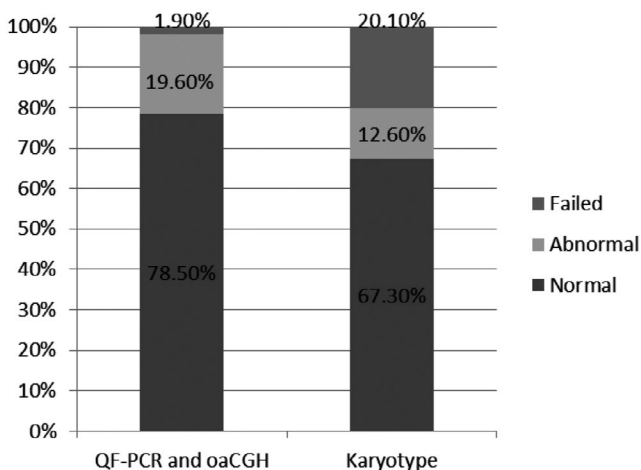


FIGURE 1 Comparison of diagnostic yield and failure rate between QF-PCR + a-CGH and karyotyping

FIGURE 2 Comparison of diagnostic yield of a-CGH with QF-PCR

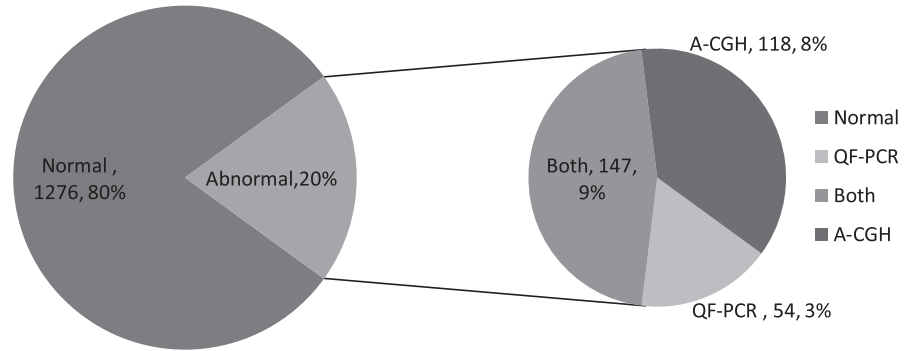


FIGURE 3 Distribution of abnormalities detected by QF-PCR and a-CGH

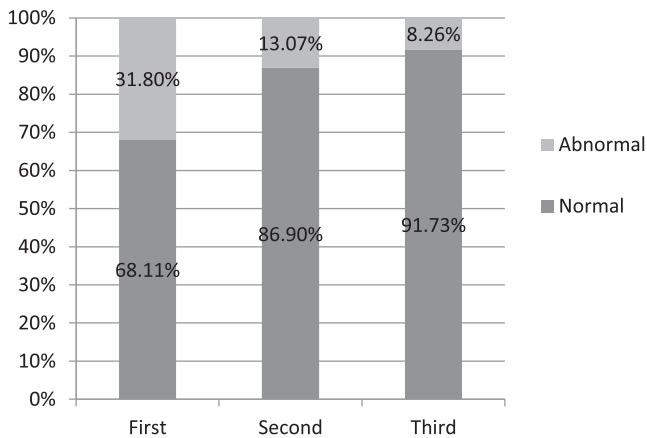
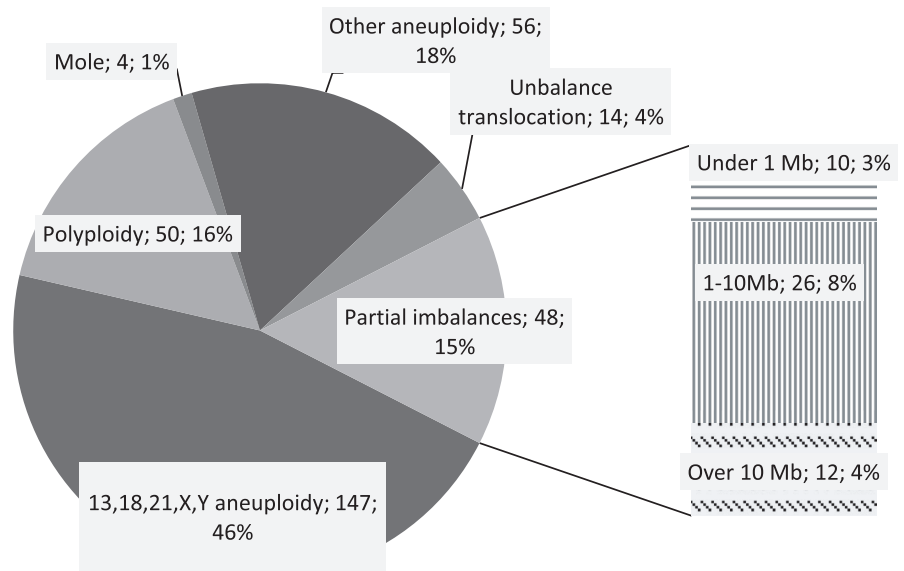


FIGURE 4 Diagnostic yields in each trimester

abnormalities in our cohort. The difference is most significant in the first trimester, less so in the second, and not present in the third. The largest cohort of 3,000 samples, by Donaghue et al., using the combination of a-CGH and QF-PCR, similar to our study, report a detection rate of 35.2% and overall 33.8% of samples were found to have causative imbalances, 31.1% were aneuploidy (Donaghue et al., 2017). Our data show an overall detection rate of 20%, 19.6%

thought to be causative, 15.9% were aneuploidy. There is no difference between their and our study's (4.1%) detection of other aberrations such as deletions/ duplications, the aberrations more common to recurrent or familial rearrangements. There is another study conducted by Wou et al., in 2016 on 1,071 product of abortion. They reported a diagnostic yield of 30.8% using QF-PCR and a-CGH. In 29.4% of cases they found justifying imbalance (Wou et al., 2016). The major difference between their study and ours detected aberrations are related to aneuploidy, the most common factor leading to first trimester loss.

We believe that there are several reasons justifying the difference in detection rate. First and foremost, we believe that this is mostly due to the high percentage of consanguineous couples. We find a statistically significant difference between CNV and aneuploidy frequency in unrelated versus related couples. Of all our cases, 34.5% are consanguineous and 55.8% are unrelated and we have no history for 9.7%. It is very interesting to note that 47/561 (8.3%) of the samples from the consanguineous couples have aneuploidies versus 141/906 (15.5%) of samples from nonconsanguineous couples, approximately one half as frequent in consanguineous couples. Also, 14/561 (2.4%) of consanguineous couples have

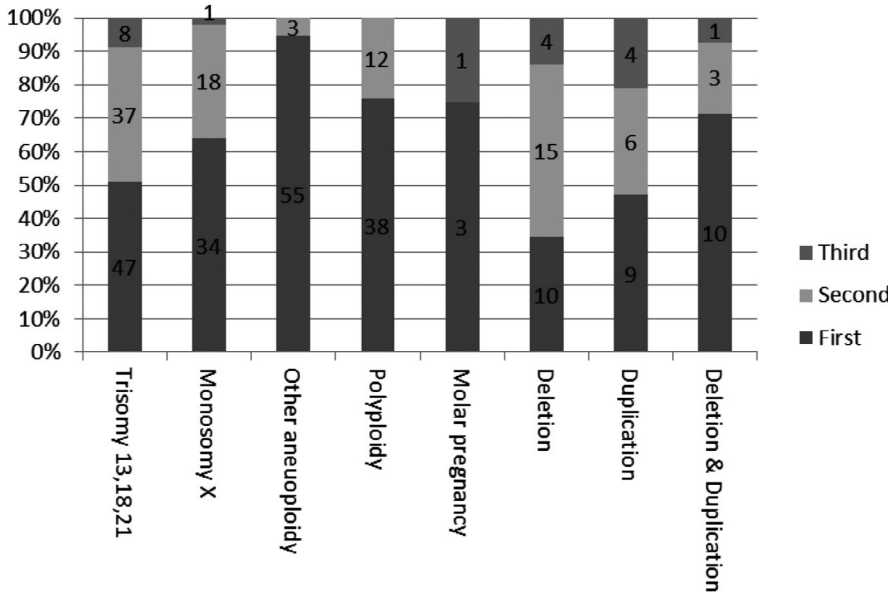


FIGURE 5 Frequency of detected abnormalities in each trimester

polyploidies compared to 32/906 (6%) of nonconsanguineous couples, approximately less than one half in consanguineous couples. Overall, the frequency of chromosomal aberrations in the consanguineous couples is 87/561 (15.5%) and in the nonconsanguineous couples is 208/906 (23%). There is a significant difference between the two groups based on their consanguinity ($\chi^2 = 11.4926$, p -value = 0.0006, Mann-Whitney 229,029, Sig = 0.001, $Z = -3.307$).

Second, there must be a difference in the referral pattern, which could explain the lower rate of aneuploidy detection in our samples. For instance, Donaghue et al used The Royal College of Obstetricians and Gynecologists (RCOG) guideline (No, 2011) for follow-up and diagnosis

of cause of abortion, where all products of pregnancy loss are sent for analysis, regardless of prior history of abortion. The largest proportion of their samples is from first trimester, when we expect to have the highest percentage of aneuploidies (Donaghue et al., 2017). In our study the largest proportion is from second trimester 45.4% ($n = 738$), where the frequency of chromosomal numerical aberrations is 9.7%. The fact that we have less, 40.4% ($n = 656$) first trimester referrals, will explain to some extent the lower number of aneuploidies of our cohort. The frequency of chromosomal numerical aberration in first trimester is 26.9%. We see this in our pattern of aberration detection as well. For instance, trisomy 16 is common in first trimester

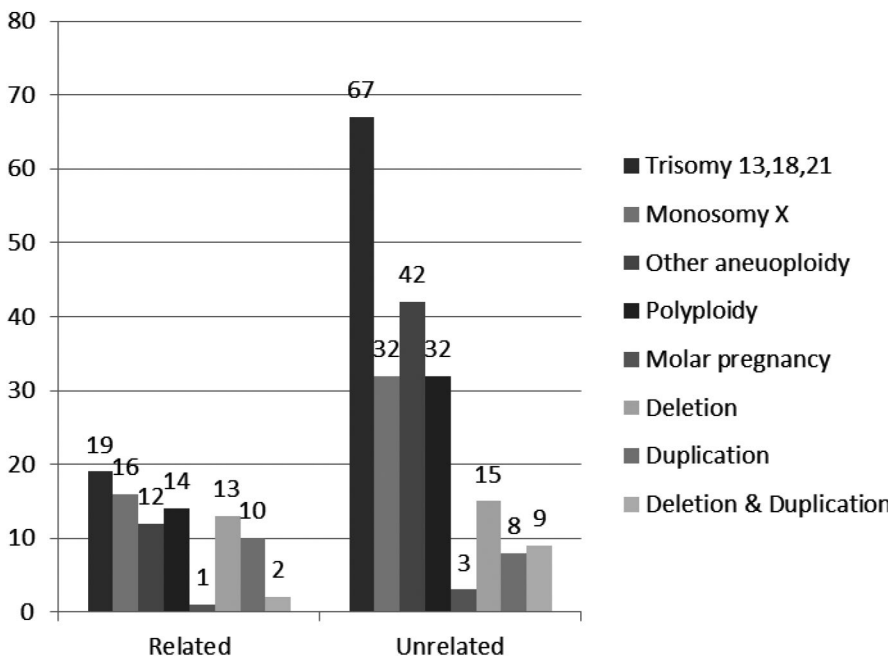


FIGURE 6 Chromosomal abnormalities in related versus unrelated couple

abortions accounting for 30% of all trisomies in abortions (Hassold, 1986; Ljunger, Cnattingius, Lundin, & Annerén, 2005), we have detected only nine cases (7.2% of all trisomies) and (4.3 of first trimester abortions).

Third, also a result of the referral pattern, we believe that many first or second time aborters have not been studied due to expense and other considerations, testing is done for recurrent pregnancy loss, where the role of aneuploidies may be less significant (Sullivan, Silver, LaCoursiere, Porter, & Branch, 2004).

Finally, 30% of the samples were sent for a-CGH following preliminary screening for the five chromosomes, excluding selectively the cases with the common aneuploidies.

We suggest that based on our findings that consanguinity would contribute to pregnancy loss and less significantly IUFD. It is highly likely that the pregnancy loss and IUFD in the consanguineous couples is caused by other genetic and immune mechanisms. It is plausible through the same mechanism by which single gene disorders have a higher prevalence of manifesting disease in consanguineous couples (Hamamy, 2012; Kahrizi et al., 2018); they can cause lethal genetic disorders leading to pregnancy loss and IUFD in these couples. We propose that further study and reports of other cohorts with similar consanguinity frequency is necessary to verify these findings. To determine the role of single gene disorders, other studies including whole exome/genome sequencing can be helpful in these couples and may help clarify the cause of their pregnancy loss and IUFD.

To our knowledge our study is the second largest study on product of abortion, Donaghue et al., being the largest with a cohort of 3,000 samples. However, none of the studies to date have had this percentage of consanguineous couples (34.5%). Therefore, this and future studies will provide a better understanding of the roles of consanguinity in pregnancy loss enabling us to better counsel and manage affected couples.

Most other studies and reviews report chromosomal aberrations in 50% of the first trimester losses, using any whole genome technique such as karyotype or combination of chromosomal microarray and QF-PCR/MLPA or SNP array. The detection of chromosomal imbalances in our first trimester cases is 31.8%.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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REFERENCES

- Bagheri, H., Mercier, E., Qiao, Y., Stephenson, M. D., & Rajcan-Separovic, E. (2015). Genomic characteristics of miscarriage copy number variants. *Molecular Human Reproduction*, *21*(8), 655–661. <https://doi.org/10.1093/molehr/gav030>
- Bell, K. A., Van Deerlin, P. G., Feinberg, R. F., du Manoir, S., & Haddad, B. R. (2001). Diagnosis of aneuploidy in archival, paraffin-embedded pregnancy-loss tissues by comparative genomic hybridization. *Fertility and Sterility*, *75*(2), 374–379. [https://doi.org/10.1016/S0015-0282\(00\)01703-9](https://doi.org/10.1016/S0015-0282(00)01703-9)
- Bell, K. A., Van Deerlin, P. G., Haddad, B. R., & Feinberg, R. F. (1999). Cytogenetic diagnosis of “normal 46, XX” karyotypes in spontaneous abortions frequently may be misleading. *Fertility and Sterility*, *71*(2), 334–341. [https://doi.org/10.1016/S0015-0282\(98\)00445-2](https://doi.org/10.1016/S0015-0282(98)00445-2)
- Borovik, C. L., Perez, A. B. A., da Silva, L. R., Krepischi-Santos, A. C. V., Costa, S. S., & Rosenberg, C. (2008). Array-CGH testing in spontaneous abortions with normal karyotypes. *Genetics and Molecular Biology*, *31*(2), 416–422. <https://doi.org/10.1590/S1415-47572008000300004>
- Cirigliano, V., Ejarque, M., Canadas, M. P., Lloveras, E., Plaja, A., del Mar Perez, M., ... Egozcue, J. (2001). Clinical application of multiplex quantitative fluorescent polymerase chain reaction (QF-PCR) for the rapid prenatal detection of common chromosome aneuploidies. *Molecular Human Reproduction*, *7*(10), 1001–1006. <https://doi.org/10.1093/molehr/7.10.1001>
- Daniely, M., Aviram-Goldring, A., Barkai, G., & Goldman, B. (1998). Detection of chromosomal aberration in fetuses arising from recurrent spontaneous abortion by comparative genomic hybridization. *Human Reproduction*, *13*(4), 805–809. <https://doi.org/10.1093/humrep/13.4.805>
- Dhillon, R., Hillman, S., Morris, R., McMullan, D., Williams, D., Coomarasamy, A., & Kilby, M. (2014). Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: A systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, *121*(1), 11–21. <https://doi.org/10.1111/1471-0528.12382>
- Donaghue, C., Davies, N., Ahn, J. W., Thomas, H., Ogilvie, C. M., & Mann, K. (2017). Efficient and cost-effective genetic analysis of products of conception and fetal tissues using a QF-PCR/array CGH strategy; five years of data. *Molecular Cytogenetics*, *10*, 12. <https://doi.org/10.1186/s13039-017-0313-9>
- Fritz, B., Hallermann, C., Olert, J., Fuchs, B., Bruns, M., Aslan, M., ... Rehder, H. (2001). Cytogenetic analyses of culture failures by comparative genomic hybridisation (CGH)—Re-evaluation of chromosome aberration rates in early spontaneous abortions. *European Journal of Human Genetics*, *9*(7), 539. <https://doi.org/10.1038/sj.ejhg.5200669>
- Goddijn, M., & Leschot, N. (2000). Genetic aspects of miscarriage. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *14*(5), 855–865. <https://doi.org/10.1053/beog.2000.0124>

- Hamamy, H. (2012). Consanguineous marriages. *Journal of Community Genetics*, 3(3), 185–192. <https://doi.org/10.1007/s12687-011-0072-y>
- Hassold, T. J. (1986). Chromosome abnormalities in human reproductive wastage. *Trends in Genetics*, 2, 105–110. [https://doi.org/10.1016/0168-9525\(86\)90194-0](https://doi.org/10.1016/0168-9525(86)90194-0)
- Jia, C.-W., Wang, L. I., Lan, Y.-L., Song, R., Zhou, L.-Y., Yu, L., ... Wang, S.-Y. (2015). Aneuploidy in early miscarriage and its related factors. *Chinese Medical Journal*, 128(20), 2772. <https://doi.org/10.4103/0366-6999.167352>
- Kahrizi, K., Hu, H., Hosseini, M., Kalscheuer, V. M., Fattahi, Z., Beheshtian, M., ... Mehvari, S. (2018). Effect of inbreeding on intellectual disability revisited by Trio sequencing. *Clinical Genetics*, 95, 151–159.
- Kearney, H. M., Thorland, E. C., Brown, K. K., Quintero-Rivera, F., & South, S. T. (2011). American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genetics in Medicine*, 13, 680. <https://doi.org/10.1097/GIM.0b013e3182217a3a>
- Ljunger, E., Cnattingius, S., Lundin, C., & Annerén, G. (2005). Chromosomal anomalies in first-trimester miscarriages. *Acta Obstetrica et Gynecologica Scandinavica*, 84(11), 1103–1107. <https://doi.org/10.1111/j.0001-6349.2005.00882.x>
- Lomax, B., Tang, S., Separovic, E., Phillips, D., Hillard, E., Thomson, T., & Kalousek, D. K. (2000). Comparative genomic hybridization in combination with flow cytometry improves results of cytogenetic analysis of spontaneous abortions. *The American Journal of Human Genetics*, 66(5), 1516–1521. <https://doi.org/10.1086/302878>
- MacDorman, M. F., & Gregory, E. (2015). Fetal and perinatal mortality: United States, 2013. *National Vital Statistics Reports*, 64(8), 1–24.
- Miller, S., Dykes, D., & Polesky, H. (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Research*, 16(3), 1215. <https://doi.org/10.1093/nar/16.3.1215>
- No, G.-T.-G. (2011). The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. *April*.
- Ozawa, N., Sago, H., Matsuoka, K., Maruyama, T., Migita, O., Aizu, Y., & Inazawa, J. (2016). Cytogenetic analysis of spontaneously discharged products of conception by array-based comparative genomic hybridization. *SpringerPlus*, 5(1), 874. <https://doi.org/10.1186/s40064-016-2594-6>
- Practice Committee of the American Society for Reproductive Medicine. (2012). Evaluation and treatment of recurrent pregnancy loss: A committee opinion. *Fertility and Sterility*, 98(5), 1103–1111.
- Rajcan-Separovic, E., Diego-Alvarez, D., Robinson, W. P., Tyson, C., Qiao, Y., Harvard, C., ... Stephenson, M. D. (2010). Identification of copy number variants in miscarriages from couples with idiopathic recurrent pregnancy loss. *Human Reproduction*, 25(11), 2913–2922. <https://doi.org/10.1093/humrep/deq202>
- Rajcan-Separovic, E., Qiao, Y., Tyson, C., Harvard, C., Fawcett, C., Kalousek, D., ... Philipp, T. (2009). Genomic changes detected by array CGH in human embryos with developmental defects. *MHR: Basic Science of Reproductive Medicine*, 16(2), 125–134.
- Robberecht, C., Schuddinck, V., Fryns, J.-P., & Vermeesch, J. R. (2009). Diagnosis of miscarriages by molecular karyotyping: Benefits and pitfalls. *Genetics in Medicine*, 11(9), 646. <https://doi.org/10.1097/GIM.0b013e3181abc92a>
- Rosenfeld, J. A., Tucker, M. E., Escobar, L. F., Neill, N. J., Torchia, B. S., McDaniel, L. D., ... Chitayat, D. (2015). Diagnostic utility of microarray testing in pregnancy loss. *Ultrasound in Obstetrics & Gynecology*, 46(4), 478–486. <https://doi.org/10.1002/uog.14866>
- Schaeffer, A. J., Chung, J., Heretis, K., Wong, A., Ledbetter, D. H., & Martin, C. L. (2004). Comparative genomic hybridization–array analysis enhances the detection of aneuploidies and submicroscopic imbalances in spontaneous miscarriages. *The American Journal of Human Genetics*, 74(6), 1168–1174. <https://doi.org/10.1086/421250>
- Stephenson, M., & Kutteh, W. (2007). Evaluation and management of recurrent early pregnancy loss. *Clinical Obstetrics and Gynecology*, 50(1), 132–145. <https://doi.org/10.1097/GRF.0b013e31802f1c28>
- Student, S. (2015). Prenatal screening for aneuploidies using QF-PCR and karyotyping: A comprehensive study in Iranian population. *Archives of Iranian Medicine*, 18(5), 296.
- Sullivan, A. E., Silver, R. M., LaCoursiere, D. Y., Porter, T. F., & Branch, D. W. (2004). Recurrent fetal aneuploidy and recurrent miscarriage. *Obstetrics & Gynecology*, 104(4), 784–788. <https://doi.org/10.1097/01.AOG.0000137832.86727.e2>
- Tabet, A. C., Aboura, A., Dauge, M. C., Audibert, F., Coulomb, A., Batallan, A., ... Tachdjian, G. (2001). Cytogenetic analysis of trophoblasts by comparative genomic hybridization in embryo-fetal development anomalies. *Prenatal Diagnosis*, 21(8), 613–618. <https://doi.org/10.1002/pd.115>
- Wou, K., Hyun, Y., Chitayat, D., Vlasschaert, M., Chong, K., Wasim, S., ... Kolomietz, E. (2016). Analysis of tissue from products of conception and perinatal losses using QF-PCR and microarray: A three-year retrospective study resulting in an efficient protocol. *European Journal of Medical Genetics*, 59(8), 417–424. <https://doi.org/10.1016/j.ejmg.2016.05.011>
- Zhang, Y.-X., Zhang, Y.-P., Gu, Y., Guan, F.-J., Li, S.-L., Xie, J.-S., ... Zhong, N. (2009). Genetic analysis of first-trimester miscarriages with a combination of cytogenetic karyotyping, microsatellite genotyping and arrayCGH. *Clinical Genetics*, 75(2), 133–140. <https://doi.org/10.1111/j.1399-0004.2008.01131.x>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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