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RESEARCH ARTICLE

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ABSTRACT

Three or more consecutive miscarriages before 20 weeks of gestation is considered as recurrent miscarriage (RM). It is a challenge for obstetricians to handle these sensitive issues which involves not only wife but also the whole family. Though recurrent miscarriage is multifactorial genetic contribution plays important role in causing recurrent miscarriage. Numerical and structural aberrations in chromosomes become the causative factor in recurrent miscarriage. Polymorphic variations are seen to be associated with RM. To find out whether Y chromosomal polymorphic variations play role in recurrent miscarriages 339 couples (678 patients) of history recurrent miscarriages were analyzed by karyotyping. Out of 339 patients in 33 (8.2%) patients Y chromosomal polymorphic variations were noticed. Amongst 33 patients in 6 (1.7%) cases Yqh+, in 21 (6.7%) Yqh-, in 5 cases inversion Y (1.2%) was found.

INTRODUCTION

Percy Malpas from Liverpool coined the term Habitual abortor for women with three or more consecutive abortions[1]. Documented data reveals 15 to 20% of all pregnancies result in recurrent miscarriages. Clinician and geneticist point of view miscarriage is a cause of concern. Not only wife suffers but also whole family undergoes social and psychological trauma. Along with anatomical, hormonal, immunological factors, genetic factors also contribute in miscarriages. 6% of chromosomal abnormalities cause recurrent miscarriages. Parental chromosomal aberrations have proved to be the reason for recurrent miscarriages.

Not only chromosomal aberrations like inversion, deletion and translocation but also heteromorphisms in chromosomes are observed in recurrent miscarriages. Chromosomes like 1, 9 and 16 show heterochromatic variations[2] and they were observed to be associated with infertility[3]. Many studies indicate that chromosomal polymorphism may cause certain clinical effect such as infertility and spontaneous abortions[4, 5]. Polymorphic variations were considered as normal for long time[6]. It was observed that heterochromatism has no effect on abortions and they are considered as normal variations[6, 7]. Heterochromatin is formed by tandemly organized highly repeated sequences of satellite DNA that do not encode proteins. So chromosomal polymorphism are considered as normal Karyotypes [8]. Wide documentation is available regarding association of variants of chromosomes in cases of recurrent abortions. Many chromosomal aberrations are involved in case of RM.

In human, Y chromosome has euchromatic region which is made up of short arm, long arm and centromere while heterochromatic region is made up of long arm Yq which varies in size. Y chromosome harbors 104 genes (21 genes on short arm, 40 on long arm, 4 on terminal region, and 39 gene position not identified). SRY gene is located on the short arm and three spermatogenesis loci are mapped on long arm known as azoospermia factors (AZFa, b, c). Out of three factors AZFc deletion is the most common cause of spermatogenic failure. It is well known that Y chromosome plays important role in sex determination and spermatogenesis[1]. However its role in RM is conflicting and not proven completely. Also, whether polymorphic variations of Y chromosome are causative factors for RM is not yet confirmed. So, we attempted to focus on incidence of Y chromosomal polymorphic variations in RM. The present study was undertaken by keeping the objective in the mind of investigating the incidence of heterochromatic variations in Y chromosome in RM.

MATERIALS AND METHODS

OBSERVATIONS AND RESULTS

1. Out of 339 couples (678 patients) in 33 (8.2%) patients Y chromosomal polymorphic variations were noticed.
2. Yqh+ was observed in 6 (1.7%) cases.

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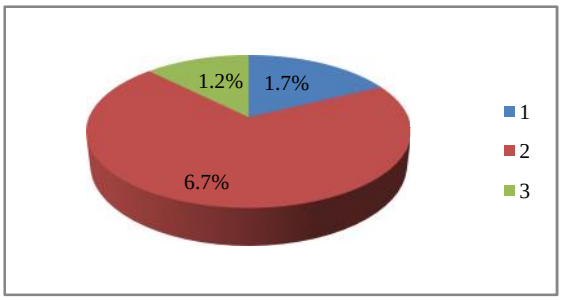
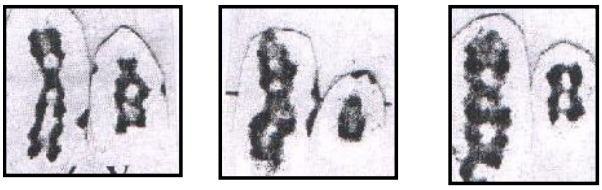
3. Yqh- was seen in 21 (6.7%) cases.
4. Inversion Y was seen in 5 (1.2%) cases.

Following chart shows percentage of Y chromosomal polymorphic variations



Following diagram shows polymorphic variations of Y chromosome in present study.



First images shows Yqh+, 2nd image shows Yqh- and 3rd image shows inversion Y chromosome

DISCUSSION

Polymorphic variations and chromosomal heteromorphism are synonymus. Normal variant, heteromorphism and polymorphism are often used interchangeably. All three usually refer to variations in human karyotype or genome that are heritable. Heteromorphism show increased heterochromatin at chromosomal telomere, short arm of chromosome and the centromere[6, 9]. Heterochromatin is defined as microscopically visible chromosome region that is variable in size, morphology and staining properties in different individuals. It is just one form of normal variation in human genome[9]. Heterochromatin located in centromere has an essential role in spindle attachment and chromosome movement, meiotic pairing [10]. When a chromatin variation occurs in these regions, it causes defects in centromere function and kinetochore assembly. This causes difficulty in homologus chromosome pairing and impacts on cell division. This could affect gamete formation [6]. Though there is a debate on the clinical significance of polymorphism of various chromosomes, cytogeneticist should not ignore there presence, occurrence and incidence. Such variants play important role in reproductive failure [11].

Polymorphic variants usually occur in long arms of 1, 9, 16 and distal 2/3rd of long arm of Y chromosome[6, 11]. Polymorphisms were more associated with chromosome 9 and Y[12].

Wide documentation of various forms of polymorphic variations of Y chromosome like long Y (Yqh+), small Y (Yqh-) and inversion Y (inv Y) reveals their incidence in RM. Yqh+ is the polymorphic variation of Y chromosome where the heterochromatin region of long arm is increased in the length. Too many DNA repeats at specific regions of Y chromosome may impact on the pairing and synapsis of X& Y chromosomes during meiosis. Increase in the long arm of Y chromosome may inhibit the expression of genes of spermatogenesis by position effect variegation and decrease reproductive capacity[3]. This was supported by putting theory that Yqh+ heterochromatin may be related to clinical abnormalities, because large Y chromosome heterochromatin represents excessive duplication of DNA that may in turn be related to errors in mitosis, gene regulation or cell differentiation, ultimately leading to spontaneous abortions[13].

Heterochromatic region of Y chromosome have been postulated to play a role in immune response during early embryo development. It is also suggested that Yqh+ may affect the viability of zygote but it does not affect fertility of its carrier[1]. Increased length of Y chromosome may be an important cause of fetal loss[14]. Several studies of families with two or more abortions have also shown a suggestive increase in frequency of chromosome variant such as a long Y in father or a large satellite in acrocentric chromosomes[15]. Increase rate of spontaneous abortion associated with Yqh+[9]. A highly statistically significant increase in the frequency of Yqh+ was observed in men whose wives had a BOH [3].

On the other side many authors deny that Yqh+ plays role in RM. Rather they say that Yqh+ in father may be unrelated to fetal loss[16], Y chromosome length variability is unassociated with reproductive problems[17], Yqh+ do not appear to have any functional or phenotypic effect[18], increased length of Y chromosome is heritable and Yqh+ has not been associated with abnormal phenotype[19].

The hypothesis explained was increased length of Y chromosome might be due to difference in the degree of contraction of chromosomes during cell division[20], Yqh+ is the result if an addition of chromosomal substance because it bears two secondary constrictions[21] and difference in the size of chromosome is a morphological feature without any functional significance[22].

Table no 1 Following table shows incidence of Yqh+ in different studies.

Name of Author	Incidence of Yqh+
S. Dubey [23]	0.13%
Abramsson L [24]	4.4%
Nagvenkar [25]	3.4%
De Ia fuente Cortes BF [26]	15.82%
Christofollini DM [27]	1.78%
Hou JW [28]	3.6%
Guluzar Aarhus [29]	0.42%
Caglayan AO [30]	1.82%
Ebru Onalan [31]	4.6%
Present Study	**1.7%**

Small or deficient heterochromatic region in long arm of Y chromosome is Yqh-.Increased or decreased length of long arm of chromosome is decided after calculating Y/F index, which is calculated as total length of Y chromosome / average total length of F group chromosomes (19 & 20). Y chromosome belongs to G group but its average total length is equivalent to the average total length of F group chromosomes. Hence the Y/F index is calculated to compare to F group. The average Y/F index is 0.95 to 1.09 [16]. Long Y (Yqh+) chromosome and short Y (Yqh-) chromosome are known to exit [32].

Table no 2 Following table shows incidence of Yqh- in different studies.

Name of author	Yqh-
S Dubey [23]	4.76%
Nagvenkar [25]	27.3%
Christofollini DM [27]	0.2%
Retief AE [33]	1.6%
Guluzar [29]	0.85%
Caglayan AO [30]	0.9%
Ebru Onalan [31]	1.9%
Present Study	**6.7%**

An inversion is a chromosome rearrangement in which a segment of a chromosome is reversed end to end. It does not involve a loss of genetic information but simply rearranges the linear gene sequence. Inversion can be pericentric where centromere is rotated and can be paracentric where breakage points are in one arm and centromere is not involved in it. Usually inversion does not cause any abnormality as long as rearrangement is balanced, however in herterozygos individuals there is an increased production of abnormal chromatids which leads to lowered fertility due to production of unbalanced gametes.

Pericentric inversion of Y was first documented by Jacobs in 1964[36]. Association between inversion Y and recurrent miscarriage is noticed by many authors. Its relative high prevalence suggested that inversion was the most common chromosomal alteration associated with repeated pregnancy loss[35]. We also found 1.2% of cases with pericentric inversion of Y chromosome. It is a rare chromosomal heteromorphism without clinical significance and does not affect sperm production[16, 36]. Though number of cases with inversion Y in RM is scanty, but its presence in RM can not be ignored.

Table no 3 Following table shows incidence of inversion Y in different studies.

Name of the author	Inversion Y
Usha Dutta [12]	0.08%
Tomomasa [34]	1 case report
Ebru Onalan [31]	0.5%
Frenny Sheth [35]	2.2%
Zhou B [37]	22%
Present Study	**1.2%**

Heteromorphism do exist and show some association in RM. It is a tip of iceberg of which the base may be broad and deep. Combine efforts of geneticist and gynaecologist will be required to search exact cause of RM. Application of advanced molecular techniques will ease the understanding of molecular basis of heteromorphism.

CONCLUSION

1. Chromosomal analysis in recurrent miscarriages is must.
2. Any heteromorphism should not be ignored.

References

1. Mala Arora, 2007, Recurrent pregnancy loss, 2nd edition, Jaypee brothers, New Dehli,, Terminology Clarified, Mala Arora, page no 3
2. Hemlata Purandare, 2011, Heterochromatic Variations and Pregnancy Losses in Human, Int J Hum Genet, 11(3): 167-175
3. Minocherhomji etal, 2009, A case control study identifying chromosomal polymorphic variations as forms of epigenetic alterations associated with the infertility phenotype, Fertil Steni, 92, 88-92
4. Madon PF, 2005,Polymorphic variants on chromosomes probably play a significant role in infertility, Reprod, Biomed, online , 11, 726-732
5. Yuce H Tekedereli I, Elyas H 2007. Cytogenetic results of recurrent spontaneous miscarriages in Turkey. Med Sci Monit, 3: CR286-CR289.
6. Hong Y, Zhou YW, Tao J, Wang SX, Zhao XM 2011. Do polymorphic variants of chromosomes affect the outcome of in vitro fertilization and embryo transfer treatment? Hum Reprod, 26: 6. 10.1093/humrep/ deq333. .
7. Hemming and Burns, 1979 Heterochromatic polymorphism in spontaneous abortions, J Med Genet, 16(5):358-62.
8. Bhasin MK 2005. Human population cytogenetics: A review. Int J Hum Genet, 5(2): 83-152.
9. Herman E Wyandt, 2011, Human chromosomes Variations: Heteromorphism and polymorphism, Springer science Business media B.V. Page-159
10. Karpen G, Endow S. Meiosis: 1998, chromosome behaviour and spindle dynamics. In: Endow S, Glover D, Editors. Frontiers in Biology. Oxford: Oxford University Press;.
11. Farcas, S., Belengeanu, V., Stoian, M., Stoicanescu, D., Popa, C., Andreescu, N., 2007, Considerations regarding the implication of polymorphic variants and chromosomal inversions in recurrent miscarriage. Jurnalul Pediatrului, 10:39-40,.
12. Usha Dutta, 2011, Cytogenetic abnormalities in 1162 couples with recurrent miscarriges in sourthern region of India, report and review, J Assist Reprod Genet, 28(2), 145-149
13. Nielsen J, 1978,Large Y chromosome (yqh+) and increased risk of abortion, clin Genet, 13(5), 415-6
14. SR Patil, 1977,A possible association of long Y chromosome and fetal loss, Human genetics, 35(2), 233-235
15. Kadotani T, Ohama K, Sato H 1969. A chromosome survey in 71 couples with repeated spontaneous abortions and stillbirth. Proc Japan Acad, 45: 180.
16. Verma RS, 1982, The clinical significance of pericentric inversion of the human Y chromosome: a rare third type of heteromorphism, J Hered, 73(3), 236-8
17. Rodriguez *et al*, 1987, c band length variabilty and reproductive wastage, Hum Genet, 75 (1), 56-61
18. Mattei MG, 2003, Heterochromatin from chromosome to protein, Atlas Genet Cytogenet Oncol Haematol, 7, 284-299
19. Makino S, 1963, A long chromosome in man, Chromosoma, 14,154-161
20. Bishop, Heritable variation in the human Y chromosome, Lancet, 1962, 18-20
21. Gripenberg, 1964, Size variation and orientation of human Y chromosome, Chromosoma 15, 618-29

22. Ghosh PK, 1975,Morphological variability of human chromosomes in two Indian populations-Rajput and Panjabis, Human genetik, 29(1), 67-68
23. S. Dubey, 2005,Cytogenetic causes of recurrent spontaneous abortions- an experience of 742 couples(1484 cases), *Indian Journal of Human Genetics*, 11(2)
24. Abramsson L, 1982,Chromosomal aberrations and male infertility, J Urol, 128: 52-3
25. Nagvenkar P, Desai K, Hinduja I, Zaveri K 2005. Chromosomal studies in infertile men with oligozoospermia and non-abstructive azoospermia. Indian J Med Res, 122: 34-42.
26. De Ia fuente Cortes BF, 2009, chromosomal abnormalities and polymorphic variants in copules with repeated miscarriage in Mexico, Reprod biomed online, 18(4), 543-8
27. Christofollini DM, 2012, Co-relation between chromosomal variants and male infertility in a population of Brazilian infertile men, Reproductive Sys Sexual disord, 1:105, 1(1)
28. Hou JW, 1999, Study of human Y chromosome polymorphism in Taiwan, Acta Paediatr Taiwan, 40: 302-304
29. Guluzar Arzu Turam, 2015, Chromosomal abnormalities and polymorphisms among couples with recurrent invitro fertilization failure, *International medical journal of Sifa university*, 2(3),49-51
30. Caglayan AO, 2013, Cytogenetic results of patients with infertility in middle Anatolia Turkey: Do heterochromatin polymorphism affect fertility? J Reprod Infertlity, 11(3)
31. Ebru Önalan Etem, *et al*. 2009, Cytogenetic analysis in infertile males with sperm anomalies *Marmara Medical Journal*, 22(3);217-224
32. D Braekeleer, 1990,Cytogenetic studies in couples experiencing repeated pregnancy losses, Human Reprod, 5: 519-28
33. Retief AE, 1984, Chromosomal studies in 496 infertile males with a sperm count below 10 million/ ml, Human Genet, 66, 162-4
34. Tomomasa H, 2000, Pericentric inversion of Y chromosome of infertile male, Arch Androl, 45(3), 181-5
35. Frenny Sheth, 2011,Clinical profile of inversion Y in people of Gujrat, West India, Int J Human Genetics, 11(4), 245-248
36. Motos Guirao MA 1989. Pericentric inversion of the human Y chromosome. An Esp Pediatr, 31: 583-587.
37. Zhou B, 2006, Mechanism of formation of a special inv (y): A case study Yichuan, 28,148-52

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