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Risk of Recurrent Miscarriage in India and the Effect of Paternal Age and Maternal Age

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ABSTRACT

Background: *A risk of miscarriage increases with increase in parental age. However many studies investigate only the effect of maternal age. This study focused on both the maternal age and paternal age effect on miscarriage.*

Method: *Couples with the pregnancy loss issue were studied with the age range 19 to 50 years. Maternal age and paternal age were analyzed together. The couples composed of a women and man both aged 20-29 years were used as reference group.*

Results: *Universally the risk of miscarriage was found to be higher if the women age was 35 years or more and man with age was 40 years or more. But due to small sample size this has not been proved in this study.*

Conclusions: *The risk of pregnancy loss increases if male and female partners are having advanced age.*

Keywords: recurrent miscarriage, parental age, age effect

Introduction

Recurrent miscarriage was initially defined as the loss of three or more clinically recognized pregnancies spontaneously during early gestation. However, the modern definition refers to the spontaneous loss of two or more consecutive pregnancies before twenty weeks of gestation (Vanilla et al, 2015).

The average life expectancy is increasing with availability of modern technology. In recent decades, women have been increasingly delaying the start of motherhood and the same trend is also seen for men because of changes in marriage patterns, lots of competition and carrier opportunities, changes in contraception use, social support, and possibly with other factors (e.g. stress, pollutants, and smoking) which are responsible for the increase in miscarriage rate. This trend has been observed in the worldwide and across all groups in the population. The association between parental age and fertility has been of significant interest to both modern and ancient scientists.

The study of age effect on human reproduction is complicated as numerous physiological changes occurring in male and females, also environmental and socioeconomic conditions influence the reproductive outcome. The purpose of this investigation was to determine whether pregnancy outcome influenced by parental age.

Most common difficult reproductive event is spontaneous abortion, with up to 10% of clinically documented conceptus are miscarried during the pregnancy (Nybo Anderson et al, 2000). Chromosomal anomalies in the zygote may result from errors during gametogenesis in either parent, during fertilization, or during the first cellular divisions of the zygote and there are many more pregnancies that fail prior to being clinically recognized. Only 30% of all conceptions result in a live birth. The risk of miscarriage is 30% after two previous losses and 35% after the third one (Imam et al,2011).

Most studies have concluded that women aged more than equal to 35 years have a higher frequency of various adverse reproductive measures such as infertility, spontaneous

abortion, pregnancy complications, congenital abnormalities than do younger women (Nybo Anderson et al, 2000; Rochebrochard et al, 2002; Homan et al, 2007; Garrisi et al, 2009; Spandorfer et al, 1998; Fretts et al, 1995). About 30-40% men in reproductive age group have quantitative or qualitative defects in sperm production (Dada et al, 2008). Similarly spontaneous abortion could be caused by paternally inherited genetic mutation, it may be more frequent with increasing paternal agebecause of continuous replication of stem cells after puberty (Slama et al, 2005).

The effect of paternal age on pregnancy outcome following natural conception has been investigated in population- based studies. In a study conducted by Slama et al. found that the spontaneous abortion rate was significantly higher in women with male partners older than 45 years compared to those whose partners were less than 25 years of age (Slama et al, 2005). Kleinhaus et al. reported that partners of women 40 years or older had an almost three-fold increase in spontaneous abortion compared to those women with a partners 25 years old or younger.
Error in gametogenesis results in the chromosomally abnormal conceptions most frequently compared to the post fertilization event. This study focused on both the maternal age and paternal age effect on miscarriage.

MATERIALS AND METHODS

The first group with 400 individuals of 200 couples (age range 19 to 50), with the history of more than two miscarriages and no live birth and as control group 200 individuals of 100 couples with one or more than one normal child (age range 20 to 50), recruited simultaneously during the study.
There was no occupational or environmental exposure to radiation (electromagnetic radiation), high temperature, toxic chemicals such as insecticides and pesticides in the patients or the controls.
Studies by Osborn et al, 2000 and Nybo Anderson et al, 2000 have shown no effect of maternal age on spontaneous abortion between the age group 20-29 years. Therefore in the present study 20-29 years age group is used as a reference for male and female. Maternal age was divided into groups such as 20-29 years, 30-34 years, 35 - 39 years and 40-50 years. Paternal age was divided into groups such as 20-29 years, 30-34 years, 35 - 39 years and 40-50 years.

RESULT:

The women had a mean age of 29.3 years, ranging between 19 and 45 years. In the control group, the mean age of women was 29.5 with a range from 20 to 45 years.
The mean number of abortion cases was ranging from 3 to 6. It was observed higher frequency of couples in the group with 3 abortions (83.5%), followed by the group with 4 abortions (10.5%) (Table 1).

Table 2 shows the distribution of paternal and maternal age of couples in case group. Out of 200 couples, 145 couples had had three abortions where male age was 40 years and above where as female age was 35 years or below.

Table 3 shows the distribution of paternal and maternal age of couples in Case and Control groups. Maximum i.e. 61 (30%) couples had males in the age range of 30-34 years and females in the age range 20-29 years. This was followed by 33 (16.5%) couples with males ranging between 35-39 years and females ranging between 30-34 years. There were 27 couples with males and females in the age range of 20-29 years.

In control groups also, maximum i.e. 32 (32%) couples had males in the range 30-34 years and females in the range 20-29 years; while 15 (15%) couples had males in the range 35-39 years and females in the range 30-34 years. The difference in the distribution of couples in two groups was statistically insignificant with p-value of 0.4154 as per Kolmogorov-Smirnov test.

Table 4 provides the distribution of couples according to number of abortions and age of males and females. Out of 200 abortions, 168 (84%) couples had three abortions, while 32 (16%) had more than 3 abortions. In the three abortions category, majority i.e. 52 (31%) couples had males in the age range of 30-34 years and females in the range of 20-29 years. This was followed by 30 (18%) couples with males in the age category of 35-39 years and females in the category of 30-34 years. There were 25 (15%) couples with both males and females in the age range of 20-29 years and having 3 abortions.

In the more than 3 abortions category, maximum i.e. 9 (28%) couples had males in the age range 30-34 years and females in the range 20-29 years; followed by 7 (22%) couples with both males and females in the age range of 30-34 years.

Table 5 gives the distribution of major chromosomal abnormalities according to gender and age criteria. In Case group, out of 200 couples, 4 (2%) males and 6 (3%) females had abnormalities. In Control group, none of the couples showed any type of abnormalities.
The distribution of polymorphic individuals according to gender and age in two groups has been shown in Table 6. In Case group, 14 (7%) males and 11 (5.5%) females showed polymorphism; while in Control group, in 100 couples, 5 (5%) males and 3 (3%) females indicated polymorphism.

The difference in the proportion of males with polymorphism in two groups was statistically insignificant with p-value of 0.6752 ($p>0.05$) using two-sample test for equality of proportions. Similarly, the difference in the proportion of females with polymorphism in two groups was statistically insignificant with p-value of 0.4981 ($p>0.05$).

DISCUSSION:
The purpose of this investigation was to determine if pregnancy outcome influenced by parental age.

In females, the number of oocytes decreases naturally through the process of atresia. According to American Society for Reproductive Medicine guidlines, the maximum complement of oocytes is 6-7 million and exists at 20 weeks of gestation in the female fetus. The number of oocytes decreases to approximately 1-2 million oocytes at birth; 300,000-500,000 at puberty; 25,000 at age 37 years and 1,000 at age 51 years (ASRM 2014).

Several studies have shown an increase in the risk of spontaneous abortion in women age 35years or more than 35 years (Osborn et al,2000; Nybo Anderson et al, 2000). Study by Rochebrochard et al., 2002 suggested that, among women older than 35 years of age, the risk of spontaneous abortion was higher when the partner was age 40 years or older than when he was age 35–39 years. Multiple logistic regression analysis study done by Dominguez et al, 1991 showed that the maternal age begins to have an effect on pregnancy only after the 35 years of age.

Nybo Andersen et al., 2000 studied the risk of pregnancy loss according to maternal age at conception which followed a j shaped curve, with a steep increase in curve after age of 35 years. More than one fifth of all pregnancies in 35 year old women resulted in fetal loss, and at 42 years of age more than half of the intended pregnancies resulted in fetal loss.

A study by Sartorelli et al, 2001 compared men aged 23-39 years with men aged 59-74 years and found a higher frequency of sperm chromosome abnormalities in older male. Slotter et al, 2000 concludes that advancing male age is associated with a gradual and significant increase in the risk of fathering children with various chromosomal defects.
The sexual activity declines with age hence it is complex to separate the consequence of sexual behavior from age.

Advanced paternal age has been shown to result in adverse pregnancy outcome such as miscarriage, preterm delivery, low birth weight, fetal death, birth defects includes congenital heart disease, cleft lip, cleft palate, Achondroplasia etc (Bray et al.,2006). The possible causes could be structural abnormalities in sperm chromosomes (eg. Reciprocal translocations) and multiple genetic or chromosomal defects, single gene mutations. There is threefold increase in DNA damage in sperm was found in men aged 36-57 years compared to age less than 35 years (Bray et al, 2006; Templado et al, 2011; Jaleel & Khan, 2013).

Occupation, smoking, environmental exposure are the responsible factors other than age in males which influence the sperm quality and hence affects the pregnancy outcome. Stress, infection, alcohol consumption, competitive sports may result in sperm DNA fragmentation.

It is been said that the relation between spontaneous abortion is not only depend upon maternal age and the gravidity of the pregnant women but also the interval between the successive pregnancies. Therefore it is said that, couples who wish for a baby having a challenge to maintain the relative safety of having a baby with 35 years age of mother and to maintain the proper intervals between successive pregnancies.
It shows that couples who wish to reduce the risk of recurrent pregnancy loss must avoid not to wait too long to start a family and must use various contraceptive methods to enable the gaps between the successive pregnancies for a healthy reproductive life.

CONCLUSION:
This study showed a negative correlation between parental age and fertility in couples experiencing recurrent miscarriages.

Controlling for parental age effect on pregnancy outcome, we were unable to show significant effects of paternal age. So far no clear picture of the role of parental age effect on pregnancy has emerged from this study. Our sample size was insufficient to reveal effects of parental age, but our results can be understood as providing an upper boundary of any adverse pregnancy outcome.

More research in large populations and converging evidence may enable us to find out more about the mechanisms of parental age effect and their association between the pregnancy losses.

Hence older couples i.e. couples with female aged 35years or more and male aged 40 years or above should be informed that they have a high risk of miscarriage.

Couples who are planning for pregnancy need to counsel to increase the awareness about the effect of age on fertility. Women older than 35 years who failed to conceive after 6 months of attempts should receive immediate evaluation and treatment to conceive.
Detection of genetic causes helps to inform the couples with the recurrent miscarriages about the risk of transmitting genetic abnormalities that may affect the chance for successful treatment, may affect the health of offspring and can help to guide treatment options.

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References

1. Bulletti C, Flamigni C, et al. Reproductive failure due to spontaneous abortion and recurrent miscarriage. Hum Reprod Update 1996;2:118–136
2. Nybo Andersen A, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study.BMJ 2000;320;1708-1712.
3. Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentric European study. Human Reprod 2002. 17(6); 1649-1656.
4. Garrisi J, Colls P, Ferry K, Zheng X, Garrisi M, Munne S. Effect of infertility, maternal age, and number of previous miscarriages on the outcome of preimplantation genetic diagnosis for idiopathic recurrent pregnancy loss. Fertility and Sterility.2009. 92(1):288-295
5. Spandorfer S, Avrech O, Colombero L, Palermo G, Rosenwaks Z. Effect of parental age on fertilization and pregnancy characteristics in couples treated by intracytoplasmic sperm injection. Hum Reprod. 1998. 13(2); 334-338.
6. Fretts RC, Schmittdiei J, McLean FH, Usher RH, Goldman MB. Increased maternal age and the risk of fetal death. The New England Journal of Medicine.1995. 333(15):953-957
7. Vanilla S, Dayanand C, Kotur P, Kutty M, Vegi P. Evidence of Paternal N5, N10 - Methylenetetrahydrofolate Reductase (MTHFR) C677T Gene Polymorphism in Couples with Recurrent Spontaneous Abortions (RSAs) in Kolar District- A South West of India.Journal of Clinical and Diagnostic Research 2015; 9(2): 15-18
8. Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan S. Influence of Paternal Age on the Risk of Spontaneous Abortion. Am J Epidemiol 2005;161:816–823
9. Homan G, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Human Reproduction Update 2007, 13(3); 209–223.
10. Kleinhaus K, Perrin M, Friedlander Y,Paltiel O, Malaspina D, Harlap S. Paternal Age and Spontaneous Abortion. Obstet Gynecol 2006;108:369–377
11. Osborn J, Cattaruzz M, Spinelli A. Risk of spontaneous abortion in Italy, 1978-1995, and the effect of maternal age, gravidity, amrital status and education. Am J Epidemoil.,2000. 151,98-105.

12. V. Domìnguez, E. Calle, P. Ortega, P. Astasio, J. Valero De Bernabè, J. Rey Calero Source: European Journal of Epidemiology, Vol. 7, No. 2 (Mar., 1991), pp. 171-174
13. Sloter E, Marchetti F, Eskenazi B, Weldon R, Nath J, Cabreros D, Wyrobek A. Frequency of human sperm carrying structural aberrations of chromosome 1 increases with advancing age. Fertil Steril 2007;87:1077–86.
14. Sartorelli E, Mazzucatto L, De Pina Neto J. Effect of paternal age on human sperm chromosomes. Fertil Steril. 2001.76;1119-1123
15. American society for reproductive medicine committee opinion no 589., Female age-related fertility decline. Fertil Steril, 101(3):633-634(2014)
16. Jaleel R, Khan A. Paternal factors in spontaneous first trimester miscarriage. Pak J Med Sci 2013;29(3):748-752.
17. Bray I, Gunnell D, Smith G.Advanced paternal age: How old is too old?. J Epidemiol Community Health 2006;60:851–853.
18. Templado C, Donate A, Giraldo J, Bosch M, Estop A. Advanced age increases chromosome structural abnormalities in human spermatozoa. European Journal of Human Genetics (2011) 19, 145–151
19. Imam SN, Shamsi MB, Kumar K, Deka D, Dada R. Idiopathic Recurrent Pregnancy Loss Role of Paternal Factors; A Pilot Study. J Reprod Infertil.2011;12(4):267-276.

(Figures and Tables)

TABLE 1- Number of Abortions of Women's With History of Recurrent Miscarriage.

No of Abortions	No. of Couples	Percentage
3	167	83.5
4	21	10.5
5	10	5
6	2	1
Total	**200**	**100**

TABLE 2- Distribution of Couples According To Number of Abortions and Age Criteria For Males And Females In Case Group

		Cases (couples=200)		
Variable	**Age category**	**F <= 35**	**F > 35**	**Total**
Abortions				
3	M <= 40	145	8	153
	M > 40	11	3	14
	Total	156	11	167
>3	M <= 40	27	1	28
	M > 40	2	3	5
	Total	29	4	33

TABLE 3- Distribution Of Couples According To Age Criteria For Males And Females In Two Groups

	Case (couples=200)					Control (couples=100)			
Maternal age (year) →	**20 - 29**	**30 - 34**	**35 - 39**	**>= 40**		**20 - 29**	**30 - 34**	**35 - 39**	**>= 40**
Paternal age (year)↓									
20 – 29	27	0	0	0		8	0	0	0
30 – 34	61	19	2	0		32	18	1	0
35 – 39	16	33	15	0		9	15	5	0
>= 40	3	11	11	2		0	4	5	3

TABLE 4-Distribution of Couples According To Number of Abortions and Age Criteria for Males and Females In Case Group (n=200)

Variable	**Maternal age →**	**20 - 29**	**30 - 34**	**35 - 39**	**>= 40**
Abortions	**Paternal age ↓**				
3 (n=168)	20 - 29	25	0	0	0
	30 - 34	52	12	1	0
	35 - 39	15	30	11	0
	>= 40	3	10	8	1
> 3 (n=32)	20 - 29	2	0	0	0
	30 - 34	9	7	1	0
	35 - 39	1	3	4	0
	>= 40	0	1	3	1

TABLE 5-Distribution of Abnormalities According To Gender and Age Criteria In Two Groups

Abnormality	Age category	Cases (n=200)	Control (n=100)
Males	20 - 29	0	0
	30 - 34	1 (0.5%)	0
	35 - 39	1 (0.5%)	0
	>= 40	2 (1%)	0
	Total	4 (2%)	0
Females	20 - 29	4 (2%)	0
	30 - 34	0	0
	35 - 39	2 (1%)	0
	>= 40	0	0
	Total	6 (3%)	0

TABLE 6- Distribution Of Polymorphic Variation According To Gender And Age In Study Subjects.

Polymorphic variation	Age category	Cases (n=200)	Control (n=100)
Males	20 – 29	1 (0.5%)	0
	30 – 34	6 (3%)	4 (4%)
	35 – 39	6 (3%)	1 (1%)
	>= 40	1 (0.5%)	0
	Total	**14 (7%)**	**5 (5%)**
Females	20 – 29	6 (3%)	0
	30 – 34	2 (1%)	1 (1%)
	35 – 39	2 (1%)	2 (2%)
	>= 40	1 (0.5%)	0
	Total	**11 (5.5%)**	**3 (3%)**