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Recurrent Pregnancy Loss – Is It Advanced Age or Advanced Maternal Mother's Age of Young Women a Major Contributing Factor

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Abstract : *Advanced maternal age is considered as a major influencing factor for recurrent pregnancy loss (RPL). However contrarily incidence of young women experiencing RPL is increasing drastically. Maternal age and maternal mother's age are analyzed against the control group considering the reproductive history and pedigree analysis to study the association between RPL and advanced age. A total of 400 women aged 18-40 years with the history of two or more pregnancy loss attending different hospitals and clinics in Mysore city, South Karnataka were recruited. As control group 400 women of similar age range with no previous history of RPL were recruited. In this study, 84% of the pregnancies intended to be carried to term ended with fetal loss within 30 years of age. Surpringly 67.25 % of the maternal mothers were observed to be above above 35 years of age when they gave birth to young mothers with RPL. The risk of a spontaneous abortion was observed to be 64.6% in women aged 18–25 years and only 16% with age 30-40 years. Therefore not alone advanced maternal age but advanced maternal mother's age should be considered as a major risk factor for RPL.*

Keywords - *advanced age, maternal mother, pedigree analysis, recurrent pregnancy*

I. Introduction

Recurrent pregnancy loss (RPL) by definition is two or more confirmed uterine pregnancy loss (PL) prior to 20 weeks of gestation [1]. Although 15 percent of all clinically recognized pregnancies between 4 and 20 weeks will undergo pregnancy loss, the true loss rate is more than 50 percent, since the conception gets unrecognized before four weeks [2]. The most common etiology during first trimester is regarded as chromosomal abnormality which could be due to the aberrations in egg or sperm cell [3]. This could also be due to defect in chromosomal segregation process during the formation of a zygote [4]. Other etiologies of PL causes include anatomic abnormalities, endocrine disorders, infections or maternal health problems, lifestyle such as smoking, drugs, malnutrition, excessive caffeine and exposure to radiation or toxic substances which can hinder the process of implantation [5]. Despite maternal and paternal age, maternal mother's age could be a major etiology for RPL.

In recent decades, an increase in mean maternal age at childbirth in most high-resourced countries has been observed evidently. Advanced maternal age which is considered above 35years is being strongly associated with several adverse maternal and perinatal outcomes [6]. Even though ample of literature is available on RPL, data from contemporary population-based cohorts that controls for demographic variables known to influence perinatal outcomes is limited. Contrarily in the present study, a drastic increase in the frequency of RPL among women within the age of 18-35 years was evident. Further when family history was carefully analyzed through pedigree analysis it was ascertained that females experiencing RPL was the younger or the youngest child of the entire sibling in most of the cases. Most striking observation was that exceptionally maternal mother's age was above 35 years of age when they gave birth to these young mothers with RPL. In this regard the present study was designed to evaluate the obstetric outcome in women experiencing RPL in correlation with maternal mother age.

II. Materials and Methods

The study was conducted after obtaining Institutional ethical committee clearance (IHEC-UOM No.52/PhD/2011-12). A total of 400 women attending different hospitals and clinics in Mysore city, South Karnataka were recruited for the present study .The age ranged from 18-40 years with a history of 2 or more (mean ± SD: 3.3 ± 1.8, range 2–8) previous pregnancy losses.

Control subjects (n = 400) were women of similar age (mean ± SD: 33.3 ± 4.7 years, range 24–41) with no previously recognized miscarriage, and with no clinical evidence of endocrine uterine or chromosomal abnormality.

All the subjects were recruited after informed written consent was obtained. Subjects were ascertained through gynecologist of different hospitals and clinics in and around Mysore. A detailed family, occupational, reproductive and clinical histories were recorded through pre designed performs with more than two rounds of interaction with the study subjects. Based on the family history pedigrees were constructed and later analyzed through progeny software (version 6). Statistical analysis was carried out with the help of SPSS software (version 14).

Exclusion criteria

To rule out the association of obesity or PCOD as a risk factor for RPL the body mass index (BMI) of each study and control subject was calculated using the formula weight (kg)/height (m^2) . The BMI of the study group (mean ± SD: 21.5 ± 6.4 kg/m^2) and control group (mean ± SD: 21.8 ± 1.29 kg/m^2) was recorded accordingly and women with a BMI $\geqslant$25 kg/m^2 were regarded as obese and were excluded from the study.

III. Result

In this study the age of all the study subjects and control groups were categorized into 5 groups in accordance with ascending age as 18-20, 21-25, 25-30, 31-35,and 36-40 years as depicted in table 1. Out of 400 cases studied 149 (37.2%) RPL cases were reported in women belonging to 25-30 years of when compared to control group where in maximum no of birth rate was observed in the age group of 25-30 years and only 12 (3%) cases with RPL were reported in age group of 35-40 years. It is evident that in contrast to advanced age as a major factor effecting RPL, in this study we observed a significant increase in the frequency of women with young age who are more prone to RPL (Fig 1). In earlier generations girls were married as early as 14 years or soon after the onset of menarche and by the end of their reproductive age they gave birth to more than 6-8 children. Table 2 depict the age of the subject's mother categorized according to the subject's age group when the subjects were born. In the subject group 275 (68.7%) of the cases were born when their mothers were above 35 years of age. In figure 2 it can be deduced that subject's mother's age was advanced when they gave birth to subjects. Statistical analysis was carried out using SPSS software (version 14) revealed statistically significant values when the age group of the subjects and control were subjected for one sample t-test where the p value was less than < 0.005 as depicted in table 3. Further Pearson correlation indicated the strength of association between the two groups as the correlation coefficients were very highly significant (p<0.001) with 93% of variation is observed between the groups.

A logistic regression analysis was conducted to predict the association of advanced maternal age with RPL with reference to subject and control group. Maternal mothers with advanced age were significantly higher than young maternal mothers when compared to young subject group (OR: 3.492; 95% CI: 1.375, 8.869).

Pedigree analysis clearly demonstrates the fact that advanced grand maternal age is very crucial and can have a direct correlation with RPL. Figure 3-7 are the representative pedigrees of the subjects where the probands experienceRPL even in young age and their mothers ages were above 35 years of age when the probands were born.

Figures and Tables

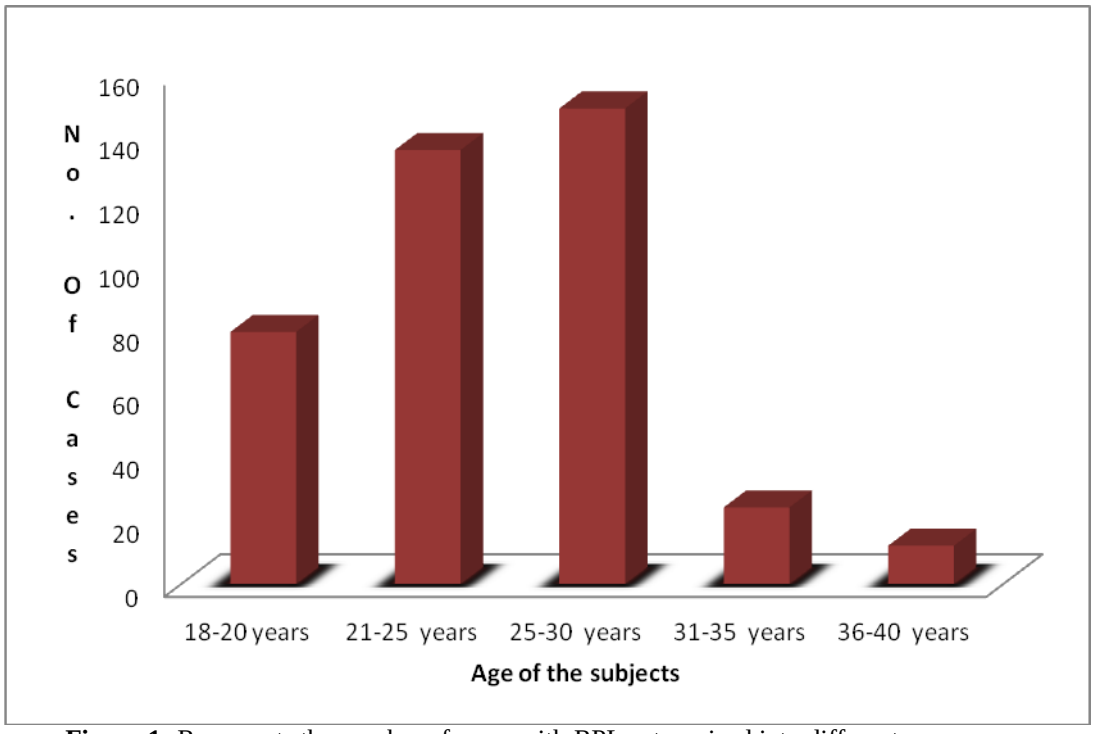

Figure 1: Represents the number of cases with RPL categorized into different age groups.

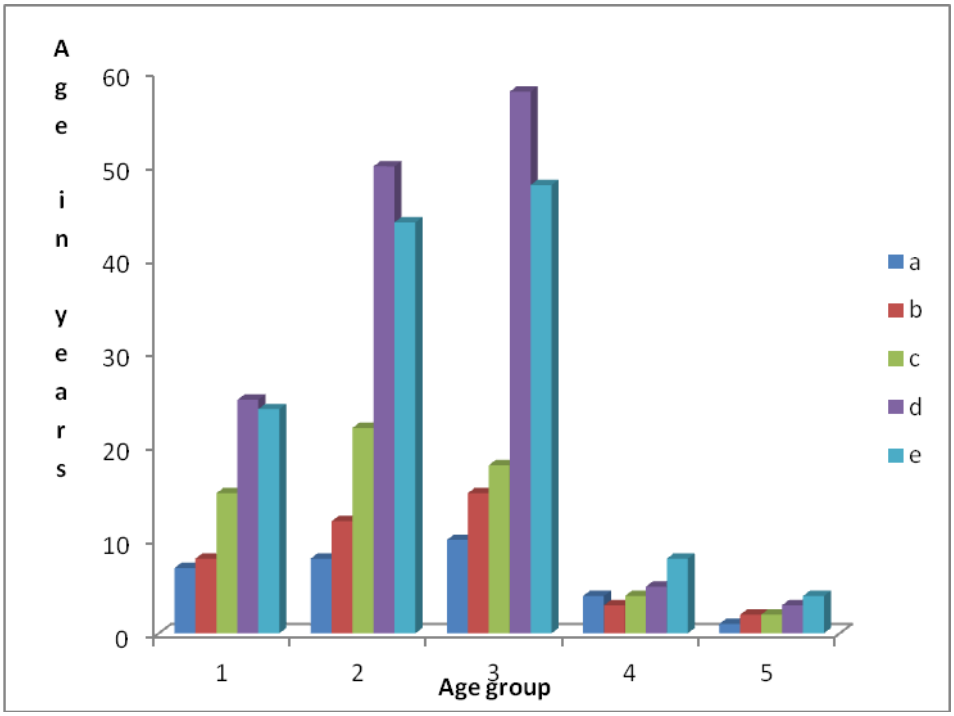

Figure 2: Representing the age of the subject against the subject's mother's age when the subject was born.

Subjects age is represented as 1:18-20 years, 2:21-25 years, 3: 25-30 ,4: 31-35, 5; 36-40 and mother's age is represented as a:18-20 years, b:21-25 years, c: 25-30, d: 31-35, d: 36-40 accordingly .

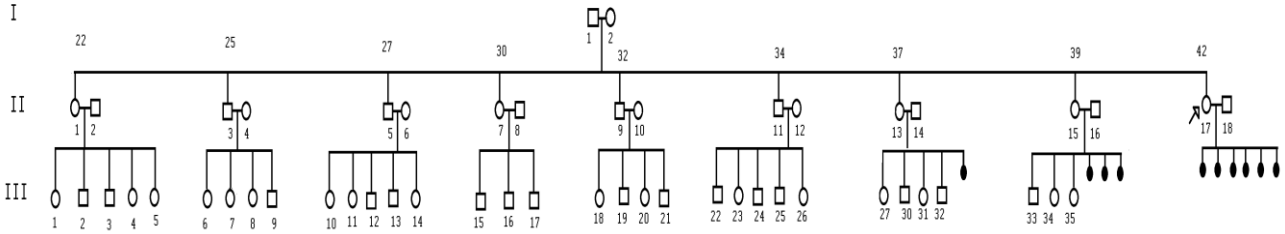

Figure 3

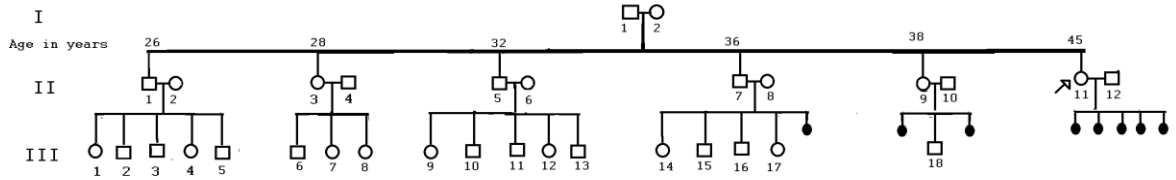

Figure 4

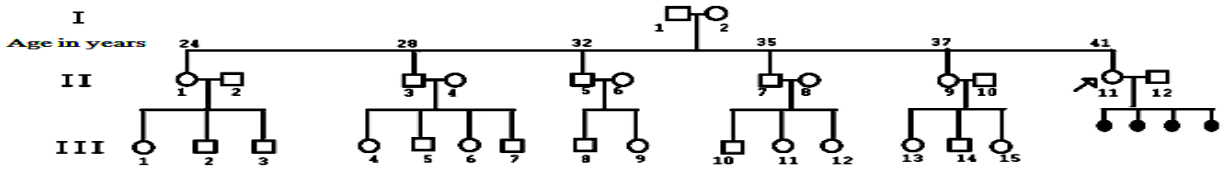

Figure 5

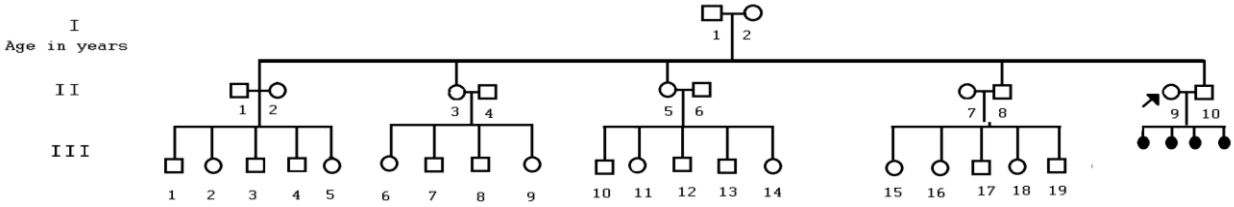

Figure 6

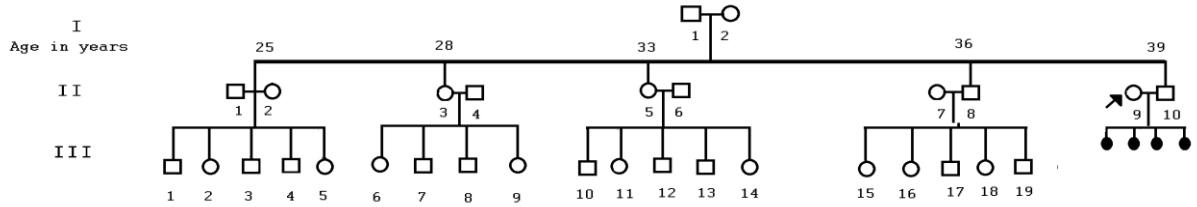

Figure 7

Figure 3-7 are the representative pedigrees of the subjects where the probands are experiencing RPL even in young age and their mothers age were above 35 years of age when the probands were born.

One-Sample *t* Test

Table 1: Represents the age of subjects categorized according to different groups and number of pregnancy loss experienced.

Age	No of Cases	No of PL	2 PL	3PL	4PL	5PL	6PL	7PL	8PL
18-20 years	79	2-4.	47	21	11	0	0	0	0
21-25 years	136	2-8.	43	32	21	13	18	4	5
25-30 years	149	2-6.	59	44	29	8	9	0	0
31-35 years	24	2-4.	12	8	4	0	0	0	0
36-40 years	12	2-4.	4	5	3	0	0	0	0
Total	400		165	110	68	21	27	4	5

PL: Pregnancy loss.

Table 2: Represents the subject mother's age categorized according to different age groups.

Subject's age in years	**No of Cases**	Mother's age in years	**No of Cases**	Mother's age in years	**No of Cases**	Mother's age in years	**No of Cases**	Mother's age in years	**No of Cases**	Mother's age in years	**No of Cases**
18-20	**79**	18-20	**9**	21-25	**12**	25-30	**18**	31-35	**25**	36-40	**24**
21-25	**136**		**12**		**18**		**24**		**50**		**44**
25-30	**149**		**18**		**23**		**21**		**58**		**47**
31-35	**24**		**6**		**4**		**6**		**5**		**9**
36-40	**12**		**1**		**2**		**2**		**3**		**4**
Total	400		46		59		71		141		128

Table 3: Analysis of one sample t test for the different age groups of RPL and maternal mothers with respect to control group

	Sig. (p<0.05)	**Exp(B)**	**95% C.I.for EXP(B)**	
			Lower	**Upper**
A	0.040	2.157	1.037	4.487
B	0.602	1.146	.687	1.911
C	**0.000**	2.266	1.519	3.381
D	**0.000**	2.266	1.519	3.381
E	**0.000**	3.862	2.641	5.648

A: 18-20 years, B:21-25 years, C:25-30, D: 31-35, E:36-40 accordingly

Table 4: Pearson correlation analysis for RPL case – control study with respect to subjects age and maternal mother's age.

Pearson **Correlations**					
N	800	800	800	800	800
	a	b	c	d	e
1	1	0.605**	0.654**	0.473**	0.288**
2		1	0.827**	0.286**	0.174**
3			1	0.309**	0.188**
4				1	0.609**
5					1

**. Correlation is significant at the 0.01 level (2-tailed). a:18-20 years, b:21-25 years, c: 25-30, d: 31-35,e: 36-40 accordingly.

Table 5: Logistic regression analyses of for RPL case – control study with respect to subjects age and maternal mother's age.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)
								Lower
a	Case	-1.086	0.285	14.486	1	0.000	0.338	0.193
	Control	-0.883	0.389	5.155	1	0.023	0.414	
b	Case	-1.086	0.285	14.486	1	0.000	v.338	0.193
	Control	-0.883	0.389	5.155	1	0.023	0.414	
c	Case	-0.441	0.179	6.073	1	0.014	0.643	0.453
	Control	-0.739	0.272	7.405	1	0.007	0.478	
d	Case	-1.324	0.210	39.733	1	0.000	0.266	0.176
	Control	0.304	0.287	1.120	1	0.290	1.356	
e	Case	-1.492	0.644	5.358	1	0.021	0.225	0.064
	Control	-1.902	0.809	5.530	1	0.019	0.149	

IV. Discussion

Previous studies demonstrate a strong correlation of advanced grand maternal age on Down's syndrome caused due to chromosomal etiologies [7-9]. However, earlier studies have upheld the correlation of advanced age with RPL but the influence of maternal mother's age on RPL is not reported till date and is often neglected. The major mechanism behind this correlation relies on the chromosomal nondisjunction during the process of meiosis which occurs after the fertilization resulting in chromosomal abnormalities is demonstrated in stem cells [10]. Previous studies have demonstrated the fact that chromosomal abnormalities are responsible for about 40-50 % of miscarriages in the first trimester. Zhang et al (2011) reported that 58.09% of the cases were with polyploids conducted on chorionic villi of 252 cases of missed abortion [11] . Similarly, the study by Kwinecka-Dmitriew et al.[12] the incidence of chromosomal abnormalities in PL was observed to be

37.5% (45/120) of the cases . The incidence was 42.4% (25/59) in the first miscarriages and 32.8% (20/61) in recurrent miscarriages. Non disjunction is very crucial during the segregation of exact number of chromosome and any discrepancies results in abnormal chromosomal segregation in zygote which might ultimately lead to PL [13,14]. Small structural chromosomal abnormalities like short tandem repeats, single nucleotide polymorphisms and copy number variants are known as polymorphisms. These generally have no clinical significance and are known to be responsible from most of the genetic variations in populations. Recent studies have mentioned the possible association of polymorphisms with reproductive failure and recurrent spontaneous miscarriages [15].

In India girls are married as early as 18 years of age and they produce more number of kids until the age of 40 or more. In the present study the subjects experiencing RPL were recorded to be under the age of 35 years. However the pedigree analysis clearly demonstrates that these young women were born during the advanced age of their mothers. Though no significant phenotypic abnormalities were observed in the study subjects however, genetic changes in the primordial cells entering the germ line which will be passed on to the fetus. During the development of such effected fetus presence of chromosomal aberrations inhibits the further developmental stages therefore these embryos are non viable resulting in PL[16]. Proteins like spindle associated proteins, factors responsible for resting of oocyte, chiasma-binding proteins, DNA repair enzymes, etc are very essential for the precise meiotic segregation [17]. At the advanced age reproductive system may not be capable of synthesizing these functional proteins accurately which are needed for proper meiotic segregation in the germ cells of her daughter. This non-availability or non-functioning of proteins leads to impairment in the meiotic process, which in turn results in nondisjunction of chromosomes in the oocyte of the daughter [18]. This event could take place during the embryogenesis of the expecting mothers of the embryo when she was in her mother's womb which affects the meiosis when she gets conceived ultimately resulting in RPL. In this study, 336 (84%) of the pregnancies intended to be carried to term ended with fetal loss within 30 years of age

Significant revelation observed in our study accounts to the fact that 269 (67.25 %) of the maternal mothers were observed to above 35 years of age when they gave birth to young mothers with RPL. The risk of a spontaneous abortion was observed in 258 (64.6%) women aged 18–25 years and only 64 (16%) with age 30-40 years. To substantiate this theory statistical analysis also revealed a significant correlation between advanced maternal age their daughter experiencing RPL (Table 4 and 5)

Therefore considering these factors we put forth a significant association between the advanced ages of maternal mother which causes meiotic discrepancies which is passed on to her daughter. The statistical analysis through logistic regression have demonstrated the strong association of the effect of grand maternal age as it values were not diluted which is substantiated through pedigree analysis.

V. Conclusion

Advanced maternal age is considered as a major influencing factor in RPL. Among young women experiencing RPL broad spectrum of investigations are carried including the male factor despite in few cases concluded as idiopathic. However acquiring family history and keen analysis of pedigree is curial which could help us to deduce the underlying etiology. However the age of not the expecting parents but also the grand parents might hold the key in deducing the actual cause. The age of maternal mother at the time of birth of the mother is now considered as a risk factor for the occurrence of, not only Down syndrome or any other syndrome, but has a major influence on RPL which should not be neglected. Besides considering the advanced mother's or father's age known risk factors the age of the maternal mother at the time of birth for the mother also should be considered as an indispensable data during the evaluation.

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