INTRODUCTION

Spontaneous miscarriage is a common gynaecological condition creating an emotional crisis for the family. Around half of the spontaneous miscarriages occurring in first trimester are likely to be due to chromosomal abnormality.\(^1\) Chromosomal abnormality in the zygote may result from errors during gametogenesis, during fertilization or during first cellular division. Thus any such abnormality in the sperm could be a cause of spontaneous miscarriage. Advancing paternal age is being increasingly identified as one of the possible causes for such defects.\(^2\)\(^-\)\(^5\)

Trends towards increasing paternal age are being observed in the UK as well as USA, due to delay in marriages for attaining better socio-economic stability.\(^6\) In England and Wales, mean age at childbearing rose from 26.4 years in 1974 to 29.3 years in 2002.\(^7\) Since 1980, birth rates in United States have increased by 40% for men aged 35 – 49 years.\(^8\)

Advancing paternal age has been shown to result in subfertility, adverse pregnancy outcomes...
Paternal factors in spontaneous first trimester miscarriage

Possible mechanisms for these problems include single gene mutations, autosomal dominant diseases, structural abnormalities in sperm chromosomes (e.g., reciprocal translocations) and multiple genetic / chromosomal defects. DNA damage in sperm of men aged 36 – 57 years was found to be 3 times that of men less than 35 years.9 Male factors other than age e.g., occupation, environmental exposure and smoking have also been shown to influence sperm quality and therefore, affect early embryo loss.10 Production of reactive oxygen species e.g., by excessive stress, competitive sports, infection, alcohol, smoking, nicotine and drug abuse may result in sperm DNA fragmentation.11,12

The effect of female factors on adverse reproductive outcome is well known. But having said this, in majority of cases of spontaneous miscarriage the cause remains unidentified. Could paternal factors be responsible has not been studied in local population. This study, therefore, aimed to study the possible link of these factors with spontaneous miscarriage.

METHODOLOGY

This case control study was conducted in the Department of Obstetrics and Gynaecology, Unit V / IV, Dow Medical College and Lyari General Hospital, Karachi. Duration of study was two and half years, from November, 2007 to April, 2010. Convenient sampling was used. We studied 200 cases against 400 controls. Our inclusion criteria were pregnant women between the age of 20 – 35 years, with any parity, admitted in the Department. Women with spontaneous first trimester miscarriage were taken as cases, while those admitted for delivery beyond 24 weeks of gestation were taken as controls. Gestational age was calculated from last menstrual period and confirmed by ultrasound, done from the Department of Radiology, Lyari General Hospital. Exclusion criteria were known medical illness in either partner, induced abortion and history of recurrent miscarriages.

Data were collected on pre-designed proformas by post-graduate trainees on duty. Information was obtained from the woman regarding her age, her husband’s age, parity, gestational age, ethnic group, husband’s occupation and income, tobacco / drug abuse by woman and husband and genital tract infection in husband (suggested by urethral discharge, urethral ulcer, premature ejaculation, dysuria).

Table-I: Baseline data.

|                          | Cases            | Controls         | p     | 95% Confidence Interval |
|--------------------------|------------------|------------------|-------|-------------------------|
|                          | Mean ± SD        | Mean ± SD        |       |                         |
| Maternal age (years)     | 27.6 ± 4.9       | 26.5 ± 4.5       | 0.008 | -1.868 - 0.282          |
| Parity (n)               | 2.5 ± 2.1        | 2.7 ± 1.9        | 0.176 | -0.103 ± 0.563          |
| Paternal age (years)     | 35.5 ± 6.2       | 32.3 ± 5.4       | 0.000 | -4.131 - 2.204          |
| Income (Pakistani Rupees)| 5816.5 ± 2685    | 6777.5 ± 3030    | 0.000 | 464.3 1457              |
| Gestational age (weeks)  | 10.6 ± 1.8       | 37.5 ± 1.7       | 0.000 | 26.661 27.249           |

RESULTS

Total Gynaecology admissions during the study period were 687. Total number of miscarriages was 363, out of which 349 (96.1%) were spontaneous miscarriages. Upon further sorting, number of first trimester spontaneous miscarriages was 240 (69%), out of which 200 cases met inclusion and exclusion criteria. They were compared with 400 controls.

Table-I shows descriptive baseline data of patients. Mean maternal as well as paternal age was higher amongst the cases as compared to controls, while parity was comparable. Mean gestational age
of patients was 10.6 weeks, while controls were at term.

Paternal age was more than 35 years in 54.5% cases versus 16% controls and was more than 45 years in 1.5% and 1.2%, respectively. Majority of husbands in both groups were labourers, with income less than Rs. 5000/= . Commonest ethnic group was Balochi in more than 50%, followed by Pathans. Drug abuse history was difficult to obtain, but a substantial number of women and their husbands were using tobacco in various forms, alone or in combination (Gutka, Hukka, Pan, Beeri and Cigarette).

Table-II shows the factors studied by Spearman Bivariate Correlation. Maternal age, paternal age and genital tract infection were found to be significant risk factors. Final model (Table-III) revealed both maternal age group 31 – 35 years and paternal age > 35 years as independent risk factors.

**DISCUSSION**

The present study has demonstrated that the paternal age more than 35 years was an independent risk factor associated with spontaneous first trimester miscarriages. In order to eliminate the effect of maternal age, which is itself a known risk factor, we selected women between the age of 20 – 35 years, as this is considered to be ideal age for child bearing. Slama R, et al studied influence of paternal age on spontaneous miscarriage. They inducted women in early pregnancy and followed them to detect outcome. They found that the risk of spontaneous miscarriage with paternal age 35 or more years was 1.26 times higher (95% CI = 1.00, 1.60). The result was independent of maternal age, maternal tobacco, alcohol, caffeine and paternal tobacco use.1

Kleinhaus K conducted a case control study and concluded that odd ratio for spontaneous miscarriage was 1.6 (95% CI = 1.2 – 2.0, p = 0.003), for fathers aged 40 years or more. This risk was independent of maternal age and multiple other factors.13 Report from Reproductive Endocrinology & Infertility Committee & Collaborators states that advanced paternal age appears to be associated with increased risk of spontaneous miscarriage and some autosomal dominant conditions, autism spectrum disorder and schizophrenia. They recommend counselling of men more than 40 years of age when seeking pregnancy.14,15 Iwayoma and colleagues from Japan also found link between increasing paternal age and higher incidence of spontaneous miscarriage.16 Similar results have been reported by Veles de la Calle JF, Belloc S and Fisch H.12,17,18 Dane L published a systematic review on effect of paternal age on assisted reproductive outcomes.19 Majority of studies in this review failed to show a correlation between paternal age and spontaneous miscarriage when adjusted for maternal age, except for one study by Frattarelli et al.20 They concluded that overall pregnancy loss rate significantly increased with paternal age, 41.5% for > 50 years old and 24.4% for less than or equal to 50 years (p < 0.01; RR, 0.61; 95% CI, 0.45 – 0.84).

| Table-II: Factors associated with spontaneous miscarriage (Spearman Bivariate Correlation). |
|---------------------------------|---|---|---|
|                                  | Cases | Controls | p    |
| Maternal Age (Years)            | No  | %   | No  | %   |
| 1(REF)= 20 - 25                 | 9   | 4.5 | 46  | 11.5| 0.000|
| 2= 26 - 30                      | 47  | 23.5| 143 | 35.8|      |
| 3= 31 - 35                      | 35  | 17.5| 144 | 36  |      |
| 4= 36 - 40                      | 88  | 44  | 48  | 12  |      |
| 5= 41 - 45                      | 18  | 9   | 14  | 3.5 |      |
| 6> > 45                        | 3   | 1.5 | 5   | 1.2 |      |
| Maternal Age (Years)            | No  | %   | No  | %   |
| 1(REF)= 20 - 25                 | 82  | 41  | 198 | 49.5| 0.027|
| 2= 26 - 30                      | 73  | 36.5| 136 | 34  |      |
| 3= 31 - 35                      | 45  | 22.5| 66  | 16.5|      |
| Paternal tobacco / drug abuse    | 136 | 68  | 273 | 68  | 0.249|
| Maternal tobacco / drug abuse    | 104 | 52  | 188 | 47  | 0.951|
| Genital Tract Infection         | 13  | 6.5 | 12  | 3   | 0.043|

| Table-III: Final model (Logistic Regression). |
|---------------------------------|---|---|---|
|                                  | p  | OR | 95% CI |
| Maternal                        |    |    |       |
| Age 31-35 Years                 | 0.003| 0.360| 0.185 0.702 |
| Maternal                        |    |    |       |
| Age 36-40 Years                 | 0.000| 16.44| 6.612 40.896 |
| 41 - 45 Years                   | 0.000| 13.738| 4.376 43.127 |
| > 45 Years                      | 0.026| 7.042| 1.269 39.090 |
We selected the cutoff of 35 years for paternal age. Interestingly, none of the husbands in our study was less than 20 years, while more than 45 years were very few. Different authors have used different paternal ages. Kleinhaus K et al have studied various age groups and have found father’s age more than 40 years to be significantly associated with spontaneous miscarriage. Slama R has also studied age ranges and have found that risk of spontaneous miscarriage showed linear increase in the hazard of spontaneous miscarriage in male age between 20 and 45 years. They also observed that hazard ratio was highest with male age > 45 years compared with 18 – 24 years (HR = 1.87, 95% CI, 1.01 – 3.44). Others have used paternal age between 30 to more than 50 years.

Studies on paternal age and fertility suggest that male biological clock does exist. Similar to women, advancing paternal age results in negative effects on reproductive outcomes. Reduced semen volume, decline in sperm concentration, reduced sperm motility and morphology and reduced motile sperm count have been observed with increasing men’s age. Moreover, Luna M et al reported decline in implantation rate after assisted reproductive techniques in men > 60 years old, while Frattarelli et al and Klonoff-Cohen et al found deteriorating embryo quality. Klonoff-Cohen also found decreasing pregnancy rate with male age. Pregnancy rate was 53% for men less than or equal to 35 years, 35% for 36 – 40 years and 13% for men > 40 years. Another observation that suggests sperm abnormalities with increasing age is the higher incidence of mutations in offsprings of ageing men. Advanced paternal age is linked with poor neurocognitive scores, Apert’s syndrome, schizophrenia and autism. Ji-Yeob Choi et al in a case control study report the risk of breast cancer 1.6 fold high in offsprings of aging men, while Frattarelli et al and Klonoff-Cohen et al found deteriorating embryo quality. Moreover, Luna M et al reported decline in implantation rate after assisted reproductive techniques in men > 60 years old, while Frattarelli et al and Klonoff-Cohen et al found deteriorating embryo quality.

CONCLUSION

Paternal age more than 35 years was found to be an independent risk factor in spontaneous first trimester miscarriages.

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