The Professional Medical Journal
www.theprofesional.com

DOI: 10.17957/TPMJ/17.3799

ORIGINAL PROF-3799

CONSANGUINITY;
A RISK FACTOR FOR INTRAUTERINE DEATH?

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Article received on:
31/12/2016
Accepted for publication:
15/04/2017
Received after proof reading:
06/05/2017

ABSTRACT… Introduction: The epidemiological literature is inconsistent in its findings on association of parental consanguinity & birth outcomes. Research studies rarely look into the kin relationship of the spouses as a possible risk factor for reproductive wastage including intra uterine deaths (IUDs). **Objective:** To assess the effect of parental consanguinity on birth outcome of the offspring. **Data Source & Study Setting:** Hospital based study carried out in maternity wards of public sector & private hospitals in Hyderabad. **Study Design:** Comparative cross sectional. **Study Period:** Eight months. **Material & Methods:** Data was collected on nine hundred & sixty two new borne by filling up of questionnaire & taking notes from maternity history sheets; the intrauterine death for the current pregnancy was the outcome variable of interest & for better appraisal of the effect of consanguinity on offspring mortality, logistic regression was applied on selected proximate determinants separately for each group of consanguinity. **Results:** Higher rate of IUD was observed among consanguineous couples as compared to comparison group (12.86% v/s 2.93%). Strongly significant association of IUDs for the current pregnancy was reported among consanguineous parents, second cousins & totally inbred offspring i.e. (OR 4.89; 95% CI 2.61, 9.15; p=0.00), (OR 2.13; 95% CI 1.22, 3.72; p= 0.007) & (OR 5.07; 95% CI 3.18, 8.06; p=0.00) respectively; whereas first cousin & uncle-niece relation of spouses revealed insignificant results. **Conclusions:** Consanguinity is a critical predictor of intrauterine deaths among offspring's. At the policy level, there is need for educating people about the offspring's' health risks associated with consanguineous marriages.

Key words: Consanguinity, total inbreeding, birth outcome, intrauterine death.

Article Citation: Memon KN, Atta ur Rehman A. Consanguinity; a risk factor for intrauterine death? Professional Med J 2017;24(5):680-684. **DOI:** 10.17957/TPMJ/17.3799

INTRODUCTION

The word 'consanguineous' is derived from Latin word bearing the meaning of 'same blood'.[1] The epidemiological literature is inconsistent in its findings on association of parental consanguinity & birth outcomes. Research studies rarely look into the kin relationship of the spouses as a possible risk factor for reproductive wastage including intra uterine deaths (IUDs). Very few researchers anticipate close kinship as a risk for reproductive wastage.[2] Earlier studies have reported consanguinity as the major determinant of the observed excess intrauterine deaths in the offspring of the related parents as compared to those who in offspring of their counter parts; it was also shown that higher the degree of inbreeding, higher were the rates of perinatal deaths.[3] While searching literature we find conflicting reports regarding perinatal deaths & intrauterine deaths among consanguineous & non-consanguineous offspring[4 & 5]; additionally, a particular failing of most early studies was that very few confounders were taken into account while seeking such associations.[6] The communities with high rates of consanguinity prevalent since long times show higher rates of perinatal fetal losses including abortions, still births & intrauterine deaths.[7] This is an indirect evidence of positive association between degree of paternal inbreeding & perinatal mortality. We find no literature on unilateral parental inbreeding & its effects on perinatal health of offspring. Few studies however did not observe any significant influence of inbreeding on perinatal losses. Therefore, it has now been realized that given the quantitative evidence, the balance of benefits & harms arising from consanguinity needs reconsideration.

OBJECTIVE

To assess the effect of parental consanguinity on

intrauterine death of the offspring.

METHODOLOGY

Study Setting & design

It was a hospital based comparative cross sectional study carried out on new borns delivered in various public sector as well as private hospitals in Hyderabad city.

Sample size & sampling technique

The prevalence of consanguinity in Pakistan is estimated to be between 30-54 percent.[8] Taking this rate on an average as 40% & considering the priori confounders expected to affect the results, the total sample size was calculated as nine hundred & sixty two. The subjects were recruited from the designated hospitals through convenience sampling as per inclusion criteria within forty eight hours after delivery.

Inclusion criteria

1. Those parents who gave informed consent for their enrollment in study.
2. Those born with any physically apparent defect/malformation.
3. All singleton births.
4. Babies of all birth orders.
5. All birth intervals for the current pregnancy.
6. Maternal age between 20-45 years.
7. Babies born to mothers who had adverse obstetrical history in past.

Exclusion criteria

1. Couples not giving consent.
2. Birth interval of less than 2 years for the current pregnancy.
3. Twin pregnancy.
4. Maternal age less than 20 years. (To exclude teen age pregnancy) & >45 years.
5. Mothers having serious medical or surgical problem.

Data collection method

The data was collected by filling up of a questionnaire on two groups of newborns; one group comprising of those borne to consanguineously related parents & another group born to non-consanguineous parents; the spousal relationship was ascertained by taking detailed family history from the couples. The independent variables for the study were consanguineous status of couples, maternal & paternal inbreeding & total inbreeding. The first cousins, second cousins & uncle-niece couples were taken as consanguineous couples. The couples having blood relation beyond second cousin or those having common ancestor three or more generations above, were taken as non-consanguineous. The mother/father of the new borne who were themselves borne to consanguineous parents were labelled as maternal & paternal inbreeding respectively. The consanguineously borne subjects whose parents were also consanguineously borne, were labelled as total inbred new borne. The intrauterine death for the current pregnancy was the outcome variable of interest. Additional informations about maternal age, her educational status, socio-economic & nutritional status (in terms of Body Mass Index), previous history of unfavorable pregnancy outcomes like abortions & still births were collected as proximate covariates. Other suspected confounders like parity >3, short interval index pregnancy, maternal anemia (hemoglobin < 8 Gm/100 ml), maternal smoking & maternal addiction to betel nuts were also incorporated in the study.

Data analysis

The frequency of IUDs among both groups of the couples was computed.

For statistical analysis, SPSS version 16.0 was used. Bivariate analysis was done for individual independent variables & for better appraisal of the effect of consanguinity on offspring mortality, logistic regression was applied on selected proximate determinants for intrauterine death separately for each group of consanguinity. For multivariate analysis, the dichotomous variable indicating whether or not a couple has experienced an intrauterine death for the current pregnancy was analyzed. The following covariates showed their association to IUDs:

1. Birth interval for the current pregnancy.
2. Maternal nutritional status.
3. Ante-natal care.

4. Maternal educational status.
5. Maternal anemia.

Multiple logistic regression model was developed by incorporating these potential covariates to estimate odds ratios & 95% confidence intervals for IUDs separately for each group of parental inbreeding at p-value ≤ 0.05 fixed as cut-off level for statistical significance.

RESULTS

Group of Subjects	Subjects approached	Response Rate (%)
Consanguineous	601	91.8%
Non-Consanguineous	451	90.9%

Table-I. Response rate
Cumulative response rate: 91.4%

For purpose of data collection, one thousand & fifty two subjects were approached to reach the desired sample size of nine hundred & sixty two; the overall response rate was 91.4%.

Status	Frequency
Consanguineous	552 (57.4%)
Non-Consanguineous	410 (42.6%)

Table-II-a. Consanguinity status n=962

Borne To	Frequency
First Cousins	264 (47.82%)
Second Cousins	230 (41.67%)
Uncle-niece relation	58 (10.51%)

Table-II-b. Types of consanguinity n=552

Inbreeding Profile	Frequency	
Maternal inbreeding	Yes No	440 (45.74%)* 522 (54.26%)
Paternal inbreeding	Yes No	469 (48.75%) 493 (51.25%)
Both parents inbreeding	Yes No	237 (24.64%) 725 (75.36%)

Table- II-c. Parental inbreeding profile n=962
***row percentages were calculated.**

Inbreeding Profile	Frequency	
Total inbreeding	Yes No	204 (21.20%) 758 (78.80%)

Table-II-D. Cummulative inbreeding profile n =962
***row percentages were calculated.**

The rate of intrauterine deaths was calculated as 8.62%. Higher rate of intrauterine deaths was observed among consanguineous couples as compared to those in comparison group (12.86% v/s 2.93%).

The results showed strongly significant association of intrauterine death for the current

Spousal Relation		Intrauterine Death for current pregnancy	*Odds Ratio	95% CI Lower-Upper	P-value
Consanguinity	Yes 552 (57.4%) No 410 (42.6%)	71 (12.86%) 12 (2.93%)	4.89	2.61 - 9.15	0.000†
First Cousin	Yes 264 (47.82%) No 288 (52.18%)	43 (16.29%) 28 (9.72%)	0.55	0.33 - 0.92	0.02
Second Cousin	Yes 230 (41.67%) No 322 (58.33%)	19 (8.26%) 52 (16.14%)	2.13	1.22 – 3.72	0.007†
Uncle-niece	Yes 58 (10.51%) No 494 (89.49%)	09 (15.52%) 62 (12.55%)	0.78	0.36 – 1.66	0.52
Mother Inbred	Yes 440 (45.74%) No 522 (54.26%)	57 (12.95%) 26 (4.98%)	2.83	1.75 – 4.60	0.000†
Father Inbred	Yes 469 (48.75%) No 493 (51.25%)	60 (12.79%) 23 (4.67%)	2.99	1.82 – 4.93	0.000†
Both parents inbred	Yes 237 (24.64%) No 725 (75.36%)	47 (19.83%) 36 (4.96%)	4.73	2.98 – 7.52	0.000†
Total Inbred	Yes 204 (21.20%) No 758 (78.80%)	44 (21.57%) 39 (5.15%)	5.07	3.18 – 8.06	0.000†

Table-III. Association of inbreeding & intrauterine death
***Non adjusted Odds ratios**
†Significant associations

pregnancy among consanguineous parents (OR 4.89; 95% CI 2.61, 9.15; p=0.000), second cousin (OR 2.13; 95% CI 1.22,3.72; p= 0.007), maternal inbreeding(OR 2.83;95% CI1.75,4.60; p=0.000), paternal inbreeding (OR 2.99, 95% CI 1.82,4.93; p=0.000) , both parents inbreeding (OR 4.73; 95% CI 2.98,7.52; p=0.000) as well as total inbreeding (OR 5.07; 95% CI 3.18,8.06; p=0.000); whereas first cousin & uncle-niece relation of spouses revealed insignificant association with the intrauterine deaths of the offspring.

Spousal Relation		Intrauterine Death for current pregnancy	*Odds Ratio	95% CI Lower-Upper	p-value
Consanguinity	Yes 552 (57.4%) No 410 (42.6%)	71 (12.86%) 12 (2.93%)	4.35	2.30 – 8.25	0.000†
Second Cousin	Yes 230 (41.67%) No 322 (58.33%)	19 (8.26%) 52 (16.14%)	2.53	1.18 – 5.41	0.016†
Mother Inbred	Yes 440 (45.74%) No 522 (54.26%)	57 (12.95%) 26 (4.98%)	2.67	1.64 – 4.36	0.000†
Father Inbred	Yes 469 (48.75%) No 493 (51.25%)	60 (12.79%) 23 (4.67%)	2.83	1.70 – 4.71	0.000†
Both parents inbred	Yes 237 (24.64%) No 725 (75.36%)	47 (19.83%) 36 (4.96%)	4.49	2.80 – 7.21	0.000†
Total Inbred	Yes 204 (21.20%) No 758 (78.80%)	44 (21.57%) 39 (5.15%)	4.76	2.96 – 7.66	0.000†

Table-IV. Estimated risk for intrauterine death for current pregnancy in consanguineous new borne
***Adjusted Odds ratio for birth interval < 2 years for the current pregnancy, maternal malnutrition, infrequent ante-natal checkup, maternal illiteracy & maternal anemia.**
†Significant associations

DISCUSSION

With few geographical exceptions, consanguineous pattern of marriage in Pakistan is reported to range between 31.1 to 60 percent.[9] We found this rate as 57.4%. The rate of intrauterine deaths was calculated as 8.62%.The higher rate of intrauterine deaths were also reported in older research on consanguineous as compared to non-consanguineous offspring (OR 4.2 against 2.8, p<0.01).[10]

The results of logistic regression model estimates confirm the findings of bivariate analysis. It is interesting to observe that in bivariate analysis, the odds ratio goes on increasing from single parent consanguinity to both parent consanguinity & it is maximum in total consanguinity of the progeny. The similar trend is found in adjusted odds ratios. These results are in agreement with findings of other reports investigating the effect of inbreeding on reproductive wastage with special emphasis on intrauterine deaths. Maghsoudlou, Cnattingius et al endorsed our findings in a population based case control study demonstrating positive association between parental inbreeding & risk of intrauterine deaths & still births (OR 1.53; 95% CI 1.10-2.14 p=<0.01).[11] There have been other studies supporting our findings demonstrating an increase in risk of intra uterine deaths as the degree of parental consanguinity increases. A prospective study revealed that non-consanguineous couples had fewer stillbirths (2.6 vs 6.9% *P*=0.017; adjusted *P*=0.050.[12] Another prospective study conducted in India on the same issue revealed maternal infrequent ante-natal visits, illiteracy & short interval pregnancies as strong covariates in finding out association of consanguinity & adverse pregnancy outcomes.[13] In that study after controlling for these background confounders, the relative risk of having intrauterine death was higher among consanguineous group of mothers as compared to their counterparts (RR1.59, 95%CI 1.15, 2.18; p=<0.01).

Another interesting finding in the study is that the adjusted odds ratios reported from logistic regression model for all degrees of consanguinity were lower than those obtained in bivariate

analysis; this difference reveals the role of covariates already identified in preliminary analysis of other socio-demographic characteristics of the study population. Contrary to these findings, multiple other studies in highly consanguineous world populations like Sudan[14], Saudi Arab[15] & Jordan[16] have noted that pre pregnancy loss had no significant association with consanguinity.

CONCLUSIONS

Consanguinity is a critical predictor of intrauterine deaths among progeny of consanguineous couples. Because of the possibility of controlling the confounders, the study gives clear indications for prevention. At the policy level this study highlights the need for educating people about the offspring's' health risks associated with consanguineous marriages.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Khalida Naz Memon	Conception & Design of the work, acquisition, analysis & interpretation of data, write up of the manuscript.	
2	Prof. Aneela Atta Ur Rahman	Critical revising of the manuscript, final approval of the version for publication, ensuring the integrity of manuscript.