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Consanguinity is Strongly Associated with Fetal Congenital Anencephaly

Alia A Shuaib[1*], Abdelrahman H Al Harazi[1]
[1]*Department of Obstetrics and Gynecology, Faculty of Medicine and Health Sciences, Sana'a University.*

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ABSTRACT
Background: Anencephaly is a type of neural tube defect characterized by abnormal development of the brain and the bones of the skull. Aims: to investigate the association between consanguinity and anencephaly which is the most severe form of neural tube defects and to assess the magnitude of the problem. Methods :A case-control study was conducted between January and December 2014, all women with anencephaly that were admitted to the obstetric department of al Thawra General hospital , Sana'a , were enrolled in this study .The subjects were divided into study (n = 72) and control groups (n=25). Results: From a total of 11283 deliveries, 97 women were having anencephaly giving the overall incidence as 8.5/1000 births. We found significant number (74.2%) of these affected women had consanguineous marriage (95% CI 62.5-83.7; p = 0.0001). The first cousin union was present in (68%). Compared with control, the study cases were characterized by poverty, low education, absence of antenatal care, and mostly from rural setting. Conclusion: Consanguineous marriage is common in our societies and strongly associated with fetal congenital anomalies particularly anencephaly.

CONTENTS

INTRODUCTION:

Consanguineous marriages refer to union contracted between biologically related couples1. Consanguinity is traditionally favored in most of the Eastern Mediterranean region, south Asia and African countries especially in the Muslim populations 2,3. It is reported that the overall consanguinity rates in such communities collectively account for 20-50% 4,1.

Obstetrics and Gynecology, Faculty of Medicine and Health Sciences, Sana'a University, Yemen The rate in Yemen is 40-44.7% 5 and similar to Qatar and Oman, the rates are increasing in the current generation 1 . In these countries inbreeding is popular and frequently respected practice1 because the religious, social and cultural factors are still playing in favoring consanguineous union1. It is well known that offspring of consanguineous marriages are at

increased risk for rare recessive syndrome, congenital malformation and fetal, infant and child morbidity and mortality 6-7 .

The detrimental health effects associated with consanguinity are caused by the expression of recessive genes inherited from a common ancestors which probably applies to rare single gene conditions as well as to multigenes disorders with multifactorial inheritance 8,9 . Many different types of genetic disorders have been reported to be more common among consanguineous progeny such as neural tube defects (NTD) 10,8 including anencephaly which represents the most severe form of NTD 11-12 .

Aim of the study:

The aim of this study was to examine the association between consanguinity and anencephaly and to assess the magnitude of the problem.

Subjects and Methods

It was a case-control study of women with anencephalic fetuses who admitted to the delivery room for termination of pregnancy between January and December 2014 in the department of obstetrics and gynecology, Al Thawra General Hospital, Sana'a, Yemen. This study was performed according to the principles of Helsinki declaration and was approved by the hospital ethics committee. A total of 97 women diagnosed as having anencephalic fetuses were enrolled in this study. They were divided into 2 groups: those with consanguineous marriages (n=72) were assigned as the study group and the remaining cases (n=25) with non-consanguineous marriage as a control group. The control group was selected non-randomly as woman who had nonconsanguineous marriage and delivered anencephalic baby was selected as control.None was excluded from the study. The diagnosis of anencephaly was based on clinical background and ultrasonography.

A standard questionnaire was prepared that included all maternal demographics and clinical data such as maternal age , parity , gestational age , location , socioeconomic status , level of education , antenatal care , folic acid supplementation , previous history of congenital anomalies , family history of congenital malformation , level of consanguinity , drug taking and co morbidity such as DM . In addition, pregnancy complication, methods of termination, and the outcome were assessed. The questionnaire was administered through personal interview with the patients after explaining the aim and methods of the study and reassured that confidentiality is preserved. The informed consent was obtained from each participant and the questionnaire was filled by doctor incharge. Associated malformation was considered when anencephaly associated with one or more other anomalies not included in NTDs proved by neonatologist. Polyhydramnios was defined as ultrasound estimation of amniotic fluid index >25 cm. We defined the first cousins and closer as double – first cousins (in which all grandparents are shared) and first cousins in which the couple are parallel or cross cousin of either paternal or maternal descent. Distant relatives were defined as the members of the couple were relative but not with first degree relations, for example they were first cousin once removed, second cousin once removed etc .The data were analyzed using SPSS software (SPSS.Inc,Chicago,IL) version 21. The differences between the groups were calculated using t-test for parametric and Mann- Whitney-test for non-parametric data. Odd ratio and 95% confidence interval were calculated as appropriate. A p value of <0.05 is considered significant.

Results

A total of 11283 deliveries were occurred. Of these, 97 women having anencephaly. Seventy–two women (74.2%) with anencephaly had consanguineous marriage and 25 women (25.8%) had no consanguineous marriage. The notable findings was that women who had consanguineous marriages were significantly more frequent from rural areas (73.6%), non-educated (33.3%), having low socioeconomic states (55.6%), and had no antenatal care (61.1%). The differences were statistically significant between the two groups ($p < 0.05$). None of both groups was on folic acid supplementation in periconceptional period. Analysis of the levels of consanguinity among the study group revealed that (68 %) of them, the

marriage was contracted between the first cousins whereas the remaining (32 %) were with distant relatives (p<0.0001) (Table 1).

Table 1: Distribution of demographic data among the case and control groups Frequency of consanguinity among all women delivered in the hospital during the study period was (11.6%). Odds of exposure in anencephaly was 2.88, odds of exposure in non- anencephaly was 0.12467 and the odds ratio (OR) =

23.1; 95% CI 14.6003 to 36.5491, p < 0.0001.

Demographic data	**Case n=72**	**Control n=25**	**Pvalue**
Age (year)	31.9±0.22	32±0.32	0.08
Parity			
• 1	7(9.7)	3 (12)	0.7
• 2-4	47(65.3)	14 (56)	0.4
• ≥5	18(25)	8 (32)	0.4
Gestational age (weeks)	35.7±3.3	36.1±3.9	0.6
Location			
• Rural	53(73.6)	9 (36)	0.008
• Urban	19(26.4)	16 (64)	0.0012
Socio-economic status			
• Low	40(55.6)	6 (24)	0.008
• Middle	22 (30.5)	11 (44)	0.2
• High	10(13.9)	8 (32)	0.05
Education			
• Primary school	22(30.5)	3(12)	0.06
• Secondary	21(22.1)	14(56)	0.01
• University	3(4.1)	6 (24)	0.008
• None	24(33.3)	-	0.02

The proportion of consanguinity among case was 0.074 (7.4%) and the proportion of consanguinity among control group was 0.12(12%). (Table 2).

Consanguinity level			
• First cousin	49 (68)	-	
• Distant relative	23 (32)	-	
- Hx of congenital	2 (2.8)	(4)	0.7
Antenatal Care			
• Yes	28 (38.9)	21 (84)	0.000
• No	44 (61.1)	4 (16)	0.0004

Table 2: Distribution of consanguinity among women with anencephaly

Consanguinity	Anencephaly		Total
	Yes	No	
• Yes	72	1240	1312
• No	25	9946	9971
Total	97	11186	11283

Eighteen cases (25 %) of the study group had additional congenital anomalies unrelated to neural tube defects versus 3 % of the control group.

Pregnancy complications recorded in the study and control groups were anemia (31.9% versus 20 %; p=0.02) and polyhydramnios (23.6% versus 16%;p=0.4) .

Five cases (6.9%) of the study group had cesarean delivery versus two cases (8%) of the control group. The indications for cesarean section in the study cases were prolonged pregnancy in four cases and contracted pelvis in one case (2.9%).

In the control group the recent scar was the indication in two cases. Female sex was preponderance in both groups. Description of the management and outcomes are shown in table 3.

The data are present as mean± SD or n (%)

Table 3: Distribution of clinical data among the case and control groups

Clinical data : (mean± SD/ n (%))	**Case (n=72)**	**Control (n =25)**	**Pvalue**
Associated anomalies			
• Club foots	4(5.5)		
• Cleft palate± cleft lips	6(8.3)	1 (4)	0.4
• Gastrointestinal	8(11.1)	2 (8)	0.6
• Anemia	23(31.9)	5 (20)	0.02
• Polyhydramnios	17(23.6)	11 (16)	0.4
Mode of termination			
• Spontaneous	29 (40.2)	9 (36)	0.6
• Induced	38 (52.8)	12 (48)	0.1
• Cesarean	5(6.9)	2 (8)	0.8
Fetal out come			
• Alive	37 (51.3)	12 (48)	0.7
• Stillbirth	35 (48.7)	13 (52)	0.9
Sex			
• Male	28 (38.9)	11 (44)	0.9
• Female	44(61.1)	14 (56)	0.6

Odds of exposure in anencephaly =72/25= 2.8; Odds of exposure in non- anencephaly =1240/9946 = 0.12467. Odds of anencephaly in consanguinity = 72/1240 = 0.058; Odds of anencephaly in non-consanguinity = 25/9946 = 0.0025. Odds ratio (OR) = 2.88/0.12467=23.1; 95% CI 14.6003 to 36.5491, p < 0.0001.

Discussion

Consanguinity is common and continues to be preferred in Yemen due to social, cultural and economic reasons. A Consanguineous marriage is of genetic importance since close relatives have a greater chance of carrying the same alleles than do unrelated couples 13. The results of our study showed that the babies whose mothers had consanguineous marriage were 23 times more likely to have anencephaly compared to their counterparts. A study on Pakistani population reported 21% consanguinity in couples with children affected with congenital anomalies 14. It is reported that among Arabs and other Middle East countries, due to consanguinity there are adverse reproductive outcomes and increase in rates of congenital malformations including NTDs15. In the present study it is found that the most common form of consanguineous marriage was between the first cousins (68%).According to Bittle A H (2001), it is predicted for these cases to have 12.5% of their genes in common that is equivalent to inbreeding coefficient of F ≥ 0.0625 16 . This finding suggests that anencephaly and close relative marriage is strongly associated, similar to other study findings 17-19. The marriage is mostly family decision and arranged linked to significant advantages of consolidation their power and structure. Under such circumstances of long unbroken history of inbreeding among repeated generations, there is evidence that the cumulative level may be significantly higher than the value calculated for a single generation 10 .

This might explain the presence of anencephaly among consanguineous couples with distant relatives in the present study. The data on the present study confirm the previous studies reported that the highest rates of marriage to close relatives are consistently common in more traditional rural areas and among the poorest and less educated society 20 .

Likewise, the female preponderance in our sample is in line with the previous reports 21-22 though this association is recently debated 23. The proportion of anencephaly recorded in this study is comparable to that reported in other neighboring countries such as Saudi Arabia and Iran(<1/1000 births) 1,11. It is expected for the birth rate of anencephaly to decline with the introduction of prenatal ultrasonography in which the condition can be easily identified as early as 12-13 week in 100% of cases 24 . Unfortunately, the failure to achieve prenatal care was noted in the majority of cases with the resultant of late diagnosis and therefore, the possibility of unnecessary surgical intervention.

The central role of the obstetricians in such lethal and untreatable condition relies on the recognition of the risk factors for example consanguinity and thus providing preconception counseling to minimize the couples' risks of having affected offspring 8. The only other feasible option is an early detection of anencephaly so as the early interruption of pregnancy can be achieved safely.

Certainly, owing to the fact that consanguinity is long – held traditional trend in the Arab and Muslim societies and the major shift in the practice is hardly predicted in the foreseeable future, the rising public awareness on its hazard and the possible preventive measures for congenital disorders may enhance the access to the appropriate preconception and premarital counseling services 8. However, this study suggest that increasing of the public awareness of the potential hazards of birth defect particularly NTDs and the importance of periconceptional counseling of the close relative couples could result in substantial response. Such practice is cost saving compared to the cost of providing surgeries, physical therapy, and continuous care and rehabilitation for children with spina bifida. Moreover, as NTDs is life – long disabilities it is often invisible in our country because the surveillance system for birth defects is lacking as the number of pregnancies terminated due to diagnosis of NTDs is not recorded. It is therefore our suggestion that NTDs need to count, as simply counting is the first step in the analysis and prevention.

This study has some limitations. First, it is of small sample size thus, it is likely that the findings may not representative of the general population. More studies on this issue are considered priority to help understand the magnitude of the problem and therefore, planning for the appropriate preventive measures. Second, although the participants had no diabetes mellitus, were not obese or under anti-convulsant medications, we could not control for other factors shared with consanguinity for example malnutrition.

These data however showed that consanguinity was strongly associated with anencephaly, but we could not confirm that it is completely independent of those attributable factors.

Conclusion

Our study indicates that the consanguineous marriages between the first cousins was significantly high. Both close and distant unions were strongly associated with anencephaly. Less educated people are less aware of the risk associated with consanguinity and therefore less aware of the antenatal care benefits. Recommendations

The public education along with providing the appropriate facilities for preconception and premarital counseling are stressed issue that must be addressed promptly.

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